CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 76-942

Name: Ketoconazole Shampoo, 2%

Sponsor: QLT USA, Inc.

Approval Date: April 11, 2005

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-942

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-942

APPROVAL LETTER

ANDA 76-942

APR 11 2005

QLT USA, Inc.
Attention: Cheri Jones
2579 Midpoint Drive
Fort Collins, CO 80525

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated December 13, 2003, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Ketoconazole Shampoo, 2%.

Reference is also made to your amendment dated March 18, April 5, August 13, August 18, and September 2, 2004; and January 3, January 4, and January 18, 2005.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your Ketoconazole Shampoo, 2% to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Nizoral Shampoo, 2% of McNeil Consumer and Specialty Pharmaceuticals).

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Postmarketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in

draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising, and Communications, HFD-42
5600 Fishers Lane
Rockville, MD 20857

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications (HFD-42) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

Gary Buehler 4/11/05
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-942
Division File
Field Copy
HFD-610/R. West
HFD-205
HFD-610/Orange Book Staff

Approved Electronic Labeling Located at:
\\CDSESUBOGD1\N76942\N_000\2004-04-05]

Endorsements:
HFD-620/S.Patankar/
HFD-643/S.Liu/ S.H.Liu 4/5/05
HFD-617/L.Kim/
HFD-613/R.Wu/
HFD-613/J.Grace/

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F/T by

APPROVAL

4/6/05

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-942

LABELING

NDC 0781-7090-04

Ketoconazole Shampoo, 2%

For topical application only

4 fl. oz.

℞ only

Manufactured by Atrix Laboratories, Inc.
Ft. Collins, CO 80525 for
Sandoz, Inc., Broomfield, CO 80020

04457 Rev. 0 4/04

SANDOZ

4 fl. oz.

Ketoconazole Shampoo, 2%

Dosage:
One application of the shampoo should be sufficient and then intermittently as needed.

Directions for Use:
Apply the shampoo to the damp skin of the affected area and a wide margin surrounding this area. Lather, leave in place for 5 minutes, and then rinse off with water.

Active ingredient: ketoconazole, USP

Inactive ingredients: purified water, USP; sodium laureth sulfate; disodium laureth sulfosuccinate; cocamide diethanolamide, hydrochloric acid, NF; PEG-120 methyl glucose dioleate; imidurea, NF; sodium chloride, USP; sodium hydroxide, NF; fragrance; and FD&C red No. 40.

Store at a temperature not above 25°C (77°F). Protect from light.

Manufactured by:
Atrix Laboratories, Inc.
Fort Collins, CO 80525 for

Sandoz, Inc.
Broomfield, CO 80020

04458 Rev. 0 4/04

LOT: EXP:

SANDOZ

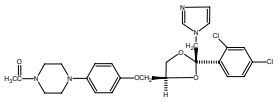
Ketoconazole Shampoo, 2%

For topical application only.

℞ only

DESCRIPTION: Ketoconazole shampoo, 2%, is a red-orange liquid for topical application, containing the broad-spectrum synthetic antifungal agent ketoconazole, USP in a concentration of 2% in an aqueous suspension. It also contains: sodium laureth sulfate; disodium laureth sulfosuccinate; cocamide diethanolamide; hydrochloric acid, NF; PEG-120 methyl glucose dioleate; imidurea, NF; sodium chloride, USP; sodium hydroxide, NF; fragrance; FD&C red No. 40; and purified water, USP.

Ketoconazole is cis-1-acetyl-4-[4-[[2-(2,4-di-chlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazine.



CLINICAL PHARMACOLOGY: Tinea (pityriasis) versicolor is a non-contagious infection of the skin caused by *Pityrosporum orbiculare (Malassezia furfur)*. This commensal organism is part of the normal skin flora. In susceptible individuals the condition is often recurrent and may give rise to hyperpigmented or hypopigmented patches on the trunk which may extend to the neck, arms and upper thighs. Treatment of the infection may not immediately result in restoration of pigment to the affected sites. Normalization of pigment following successful therapy is variable and may take months, depending on the individual skin type and incidental skin exposure. The rate of recurrence of infection is variable.

When ketoconazole shampoo, 2%, was applied dermally to intact or abraded skin of rabbits for 28 days at doses up to 50 mg/kg and allowed to remain one hour before being washed away, there were no detectable plasma ketoconazole levels using an assay method having a lower detection limit of 5 ng/mL. Ketoconazole shampoo was not detected in plasma in 39 patients who shampooed 4-10 times per week for 6 months or in 33 patients who shampooed 2-3 times per week for 3-26 months (mean: 16 months).

An exaggerated use washing test on the sensitive antecubital skin of 10 subjects twice daily for five consecutive days showed that the irritancy potential of ketoconazole shampoo, 2%, was significantly less than that of 2.5% selenium sulfide shampoo.

A human sensitization test, a phototoxicity study, and a photoallergy study conducted in 38 male and 22 female volunteers showed no contact sensitization of the delayed hypersensitivity type, no phototoxicity and no photoallergenic potential due to ketoconazole shampoo, 2%.

Mode of Action: Interpretations of *in vivo* studies suggest that ketoconazole impairs the synthesis of ergosterol, which is a vital component of fungal cell membranes. It is postulated, but not proven, that the therapeutic effect of ketoconazole in tinea (pityriasis) versicolor is due to the reduction of *Pityrosporum orbiculare (Malassezia furfur)* and that the therapeutic effect in dandruff is due to the reduction of *Pityrosporum ovale*. Support for the therapeutic effect in tinea versicolor comes from a three-arm, parallel, double-blind, placebo-controlled study in patients who had moderately severe tinea (pityriasis) versicolor. Successful response rates in the primary efficacy population for each of both three-day and single-day regimens of ketoconazole shampoo, 2%, were statistically significantly greater (73% and 69%, respectively) than a placebo regimen (5%). There had been mycological confirmation of fungal disease in all cases at baseline. Mycological clearing rates were 84% and 78%, respectively, for the three-day and one-day regimens of the 2% shampoo and 11% in the placebo regimen. While the differences in the rates of successful response between either of the two active treatments and placebo were statistically significant, the difference between the two active regimens was not.

Microbiology: Ketoconazole shampoo, 2%, is a broad-spectrum synthetic antifungal agent which inhibits the growth of the following common dermatophytes and yeasts by altering the permeability of the cell membrane: dermatophytes: *Trichophyton rubrum, T. mentagrophytes, T. tonsurans, Microsporum canis, M. audouini, M. gypseum,* and *Epidermophyton floccosum;* yeast: C*andida albicans, C. tropicalis, Pityrosporum ovale* and *Pityrosporum*

(See Reverse)

orbiculare (M. furfur). Development of resistance by these microorganisms to ketoconazole has not been reported.

INDICATIONS AND USAGE: Ketoconazole shampoo, 2%, is indicated for the treatment of tinea (pityriasis) versicolor caused by or presumed to be caused by *Pityrosporum orbiculare* (also known as *Malassezia furfur or M. orbiculare).*

Note: Tinea (pityriasis) versicolor may give rise to hyperpigmented or hypopigmented patches on the trunk which may extend to the neck, arms and upper thighs. Treatment of the infection may not immediately result in normalization of pigment to the affected sites. Normalization of pigment following successful therapy is variable and may take months, depending on individual skin type and incidental sun exposure. Although tinea versicolor is not contagious, it may recur because the organism that causes the disease is part of the normal skin flora.

CONTRAINDICATIONS: Ketoconazole shampoo, 2%, is contraindicated in persons who have shown hypersensitivity to the active ingredient or excipients of this formulation.

PRECAUTIONS: General: If a reaction suggesting sensitivity or chemical irritation should occur, use of the medication should be discontinued.

Information for Patients: May be irritating to mucous membranes of the eyes and contact with this area should be avoided.

There have been reports that use of the shampoo resulted in removal of the curl from permanently waved hair.

Carcinogenesis, Mutagenesis, Impairment of Fertility: The dominant lethal mutation test in male and female mice revealed that single oral doses of ketoconazole as high as 80 mg/kg produced no mutation in any stage of germ cell development. The Ames Salmonella microsomal activator assay was also negative. A long-term feeding study of ketoconazole in Swiss Albino mice and Wistar rats showed no evidence of oncogenic activity, when fed at doses up to 80 mg/kg/day.

Pregnancy: Teratogenic Effects: Pregnancy Category C: Ketoconazole is not detected in plasma after chronic shampooing. Ketoconazole has been shown to be teratogenic (syndactylia and oligodactylia) in the rat when given orally in the diet at 80 mg/kg/day (10 times the maximum recommended human oral dose). However, these effects may be related to maternal toxicity, which was seen at this and higher dose levels.

There are no adequate and well-controlled studies in pregnant women. Ketoconazole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Ketoconazole is not detected in plasma after chronic shampooing. Nevertheless, caution should be exercised when ketoconazole shampoo, 2%, is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: In 11 double-blind trials in 264 patients using ketoconazole shampoo, 2%, for the treatment of dandruff or seborrheic dermatitis, an increase in normal hair loss and irritation occurred in less than 1% of patients. In three open-label safety trials in which 41 patients shampooed 4-10 times weekly for six months, the following adverse experiences each occurred once: abnormal hair texture, scalp pustules, mild dryness of the skin, and itching. As with other shampoos, oiliness and dryness of hair and scalp have been reported. In a double-blind, placebo-controlled trial in which patients with tinea versicolor were treated with either a single application of ketoconazole shampoo, 2%, (n=106), a daily application for three consecutive days (n=107), or placebo (n=105), drug-related adverse events occurred in 5 (5%), 7 (7%) and 4 (4%) of patients, respectively. The only events that occurred in more than one patient in any one of the three treatment groups were pruritus, application site reaction, and dry skin; none of these events occurred in more than 3% of the patients in any one of the three groups.

OVERDOSAGE: Ketoconazole shampoo, 2%, is intended for external use only. In the event of accidental ingestion, supportive measures should be employed. Induced emesis and gastric lavage should usually be avoided.

DOSAGE AND ADMINISTRATION: Apply the shampoo to the damp skin of the affected area and a wide margin surrounding this area. Lather, leave in place for 5 minutes, and then rinse off with water.

One application of the shampoo should be sufficient.

HOW SUPPLIED:

Ketoconazole shampoo, 2%, is a red-orange liquid supplied in a 4-fluid ounce nonbreakable plastic bottle (NDC 0781-7090-04).

Storage conditions: Store at a temperature not above 25°C (77°F). Protect from light.

Manufactured By
Atrix Laboratories, Inc.
Fort Collins, CO 80525 for

Sandoz, Inc.
Broomfield, CO 80020

04456 Rev. 0 4/04

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-942

LABELING REVIEWS

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number:	76-942
Dates of Submissions:	December 13, 2003 (Electronic) and February 5, 2004
Applicant's Name:	Atrix Laboratories, Inc.
Established Name:	Ketoconazole Shampoo, 2%

Labeling Deficiencies

1. CONTAINER 4 ounce bottle (120 mL)
   "Dosage: One application...intermittently as needed." [use bold print]

2. INSERT
   a. Please note that USAN names are common nouns and should be treated as such in a text of labeling (i.e., lower case). Upper case may be used when the USAN name stands alone on labels or in the title of the package insert.
   b. CLINICAL PHARMACOLOGY, Microbiology subsection, first sentence- Revise to read: "...*floccosum;* yeast: *Candida...Pityrosporum ovale* and *Pityrosporum...*"
   c. PRECAUTIONS, Carcinogenesis, Mutagenesis, Impariment of Fertility subsection, last sentence- Revise to read: "A long-term study of...oncogenic activity, when fed at doses up to 80 mg/kg/day."

Please revise your labels and labeling, as instructed above, and 12 final printed copies.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm. Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 27		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		x	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?			
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?			
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?			X
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	

Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		x	

NOTES/QUESTIONS TO THE CHEMIST: On the container label as well as the insert labeling, the storage recommendation includes the statement "Protect from light." Does the applicant's container protect the product from light?

FOR THE RECORD:

1. MODEL LABELING-The review was based on the labeling for the reference listed drug (Nizoral Shampoo, 2%; NDA 19-927/S-014 – McNeil Consumer Healthcare; revised October 2, 1997; approved in draft October 10, 1997)

2. Packaging & Container/Closure System
   The RLD packages its product in 4 ounce bottles

   The applicant is proposing to package its product in 4 oz high density polyethylene (HDPE) bottle with a ——— cap (4-ounce Tapered Oval Plastic Bottle; Fine Ribbed Disc Cap)
   [EDR/121303/cmc/pg. 27]

3. Inactive Ingredients – There does not appear to be a discrepancy between the listing in inactives in the DESCRIPTION section of the insert labeling and the C&C Statements. [EDR/121303/cmc/pg. 3]
   Ketoconazole, USP
   PEG-120 Methyl Glucose Dioleate
   ——— Hydrochloric Acid, NF
   Imidurea, NF
   FD&C Red No. 40
   Sodium Laureth Sulfate
   Fragrance ———
   Disodium Laureth Sulfosuccinate
   Cocamide Diethanolamide
   Sodium Hydroxide, NF —
   Sodium Chloride, USP
   Purified Water, USP

4. MANUFACTURING FACILITY [EDR/121303/cmc/pg. 14]
   ATRIX Laboratories, Inc.
   701 Centre Avenue
   Fort Collins, Colorado, 80525

5. Finished product spec.: Red to orange-red; clear viscous liquid [EDR/121303/cmc/pg. 33 provides link]

6. RLD - Store at a temperature not above 25°C(77°C). Protect from light.
   ANDA – Same as RLD

7. Patent and Exclusivity for NDA 19-927 [EDR/121303/other]

   Patent Data:

Appl No	Patent No	Patent Expire Date	Drug Substance Flag	Drug Product Flag	Patent Use Code
019927	001 4942162	FEB 11,2003		II	none

   Exclusivity Data

   There is no unexpired exclusivity for this product.

Date of Review: March 15, 2004 Date of Submission: December 13, 2003 and February 5, 2004

Primary Reviewer: Ruby Wu Date: 3/15/04

Team Leader: John Grace Date: 3/17/04

cc: ANDA: 76-942
DUP/DIVISION FILE
HFD-613/RWu/JGrace (no cc)
V:\FIRMSAM\ATRIX\ltrs&rev\76942.na1.L.doc
Review

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number:	76-942
Date of Submission:	March 18, 2004 and April 5, 2004 (FPL-Electronic)
Applicant's Name:	Atrix Laboratories, Inc.
Established Name:	Ketoconazole Shampoo, 2%

APPROVAL SUMMARY:

Do you have 12 Final Printed Labels and Labeling? No. FPL was submitted electronically

1. CONTAINER – 4 ounce bottle (120 mL)
   Satisfactory in final print as of the April 5, 2004 submission. [The network path location is: \\CDSESUBOGD1\N76942\N_000\2004-04-05]

2. INSERT
   Satisfactory in final print as of the April 5, 2004 submission. [The network path location is: \\CDSESUBOGD1\N76942\N_000\2004-04-05] *(Note: There is a note to the chemist in labeling review #1 that needs to be addressed by the chemist)*

3. Revisions needed post-approval: No.

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Nizoral 2% Shampoo
NDA Number: 19-927
NDA Drug Name: Ketoconazole Shampoo, 2%
NDA Firm: McNeil Consumer Healthcare
Date of Approval of NDA Insert & supplement: NDA 19-927/S-014; revised October 2, 1997; Approved October 10, 1997
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: Side-by-side comparison with innovator labels in jacket.

PATENTS/EXCLUSIVITIES:

Patent Data:

[redacted]					
019927	001	4942162	FEB 11,2003	II	none

Exclusivity Data-There is no unexpired exclusivity for this product.

APPEARS THIS WAY
ON ORIGINAL

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 27		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		x	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			X
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?			
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?			
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?			X
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	

Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		x	

NOTES/QUESTIONS TO THE CHEMIST: *see labeling review #1*

FOR THE RECORD:

1. MODEL LABELING-The review was based on the labeling for the reference listed drug (Nizoral Shampoo, 2%; NDA 19-927/S-014 – McNeil Consumer Healthcare; revised October 2, 1997; approved in draft October 10, 1997)

2. Packaging & Container/Closure System
The RLD packages its product in 4 ounce bottles

   The applicant is proposing to package its product in 4 oz high density polyethylene (HDPE) bottle with a [redacted] cap (4-ounce Tapered Oval Plastic Bottle; Fine Ribbed Disc Cap)
   [EDR/121303/cmc/pg. 27]

3. Inactive Ingredients – There does not appear to be a discrepancy between the listing in inactives in the DESCRIPTION section of the insert labeling and the C&C Statements. [EDR/121303/cmc/pg. 3]
   Ketoconazole, USP
   PEG-120 Methyl Glucose Dioleate
   [redacted] Hydrochloric Acid, NF
   Imidurea, NF
   FD&C Red No. 40
   Sodium Laureth Sulfate
   Fragrance [redacted]
   Disodium Laureth Sulfosuccinate
   Cocamide Diethanolamide
   Sodium Hydroxide, NF [redacted]
   Sodium Chloride, USP
   Purified Water, USP

4. MANUFACTURING FACILITY [EDR/121303/cmc/pg. 14]
   ATRIX Laboratories, Inc.
   701 Centre Avenue
   Fort Collins, Colorado, 80525

5. Finished product spec.: Red to orange-red; clear viscous liquid [EDR/121303/cmc/pg. 33 provides link]

6. RLD - Store at a temperature not above 25°C(77°C). Protect from light.
   ANDA – Same as RLD

7. Patent and Exclusivity for NDA 19-927 [EDR/121303/other]

   Patent Data:

019927	001	4942162	FEB 11 2003	II	none

   Exclusivity Data

   There is no unexpired exclusivity for this product.

Date of Review: April 12, 2004 Date of Submission: March 18, 2004 and April 5, 2004

Primary Reviewer: Ruby Wu RWu Date: 4/12/04

Team Leader: John Grace JGrace Date: 4/16/04

cc: ANDA: 76-942
DUP/DIVISION FILE
HFD-613/RWu/JGrace (no cc)
V:\FIRMSAM\ATRIX\ltrs&rev\76942.ap.L.doc
Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-942

CHEMISTRY REVIEWS

ANDA 76-942

Ketoconazole Shampoo, 2%

Atrix Laboratories, Inc.

Suhas Patankar, Ph.D.
Chemistry Division I

Table of Contents

Chemistry Review Data Sheet

1. ANDA: 76-942

2. REVIEW: #1

3. REVIEW DATE: 6/21/2004

4. REVIEWER: Suhas Patankar, Ph.D.

5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

Firm	**Document Date**
Original ANDA Submission	December 13, 2003
Resubmission	February 5, 2004
(Response to Refuse to file Letter)	
Labeling Amendment	March 18, 2004
Labeling Amendment	April 5, 2004

Agency	**Document Date**
Agency Refuse to File Letter	January 27, 2004
Agency Acknowledgement Letter	February 18, 2004
(Acceptable for filing: February 9, 2004)	
Labeling Deficiency Letter	March 17, 2004

7. NAME & ADDRESS OF APPLICANT:

Name: Atrix Laboratories, Inc.

Address: 2579 Midpoint Drive

Fort Collins, CO 80525-4417

Representative: Cheri Jones

Telephone: (970) 212-4901

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Ketoconazole Shampoo, 2%

9. LEGAL BASIS FOR SUBMISSION:

a. The basis for's proposed ANDA for Ketoconazole Shampoo, 2% is the approved, RLD, Nizoral® (ketoconazole) 2% Shampoo, the subject of NDA 19-927 held by McNeil for a shampoo intended for the treatment of tinea (pityriasis) versicolor caused by or presumed to be caused by *Pityrosporum orbitculare* (*Malassezia furfur* or *M. orbiculare*).

b. According to the information published in the Electronic Orange Book, Approved Drug Products with Therapeutic Equivalence Evaluations, the RLD was approved on August 31, 1990. It is current through December 2001, there is no unexpired marketing exclusivity for NIZORAL® (ketoconazole) 2% Shampoo, under section 505(j)(4)(D) of the Act.

c. US Patent # 4,942,162 which claims the use of the listed drug to treat seborrheic dermatitis, expired on February 11, 2003.

d. Atrix Laboratories, Inc. have provided a Paragraph II certification in accordance with section 505(j)(2)(A)(vii)(III) of Title I of the FD&C Act as amended September 24, 1984, that in their opinion and to the best of their knowledge, the US Patent(s) have expired.

10. PHARMACOL. CATEGORY: Antifungal

11. DOSAGE FORM: Shampoo

12. STRENGTH/POTENCY: 2%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: Rx

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

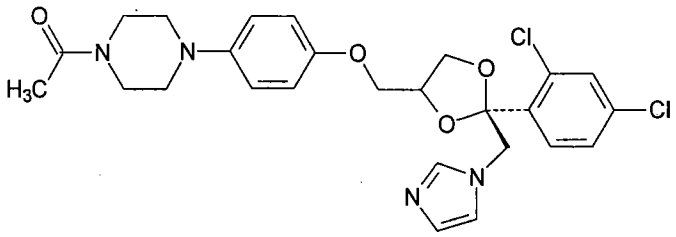
_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Formula: $C_{26}H_{28}Cl_2N_4O_4$
CAS # : 65277-42-1
Molecular Weight: 531.44

Ketoconazole. Piperazine, 1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-(1*H*-imidazole-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-, *cis*-.



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			3	Adequate	5/13/2002	Reviewed by N. Nashed
	III			4			
	III			4			
	III			4			
	III			4			
	IV			4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review

4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
ANDA	76-419	Approved 1/5/04 (Ketoconazole Shampoo 2% by Clay-Park)

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending		D'Ambrogio, J.
Methods Validation	N/A		
Labeling	Acceptable	4/16/04	Wu, R.
Bioequivalence	Pending		
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt.
__X__ Yes ____ No If no, explain reason(s) below

The Chemistry Review for ANDA 76-942

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not approvable due to minor deficiencies

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not applicable

II. Summary of Chemistry Assessments

A. Description of the Drug Substance(s) and Drug Product(s)

Ketoconazole, a synthetic imidazole derivative, is an azole antifungal agent. This USP drug substance is a white or almost white crystalline powder and is practically insoluble in water. Ketoconazole has pK_as of 2.9 and 6.5.

Atrix's proposed drug product, Ketoconazole Shampoo, 2%, is not an USP compendial item. Atrix's drug product is a red-orange, liquid containing the antifungal in an aqueous suspension. The inactive ingredients in this formulation are sodium laureth sulfate; disodium laureth sulfosuccinate; cocamide diethanolamide; hydrochloric acid, NF; PEG-120 methyl glucose dioleate; sodium chloride, USP; sodium hydroxide, NF; fragrance; FD&C red No. 40; and purified water, USP. Atrix uses Imidurea, NF as a ——— in their formulation. Atrix's Ketoconazole Shampoo, 2% is packaged in 4 fluid oz HDPE, tapered, oval bottle with a White 20 mm/ ——— fine ribbed disc cap.

The labeling does not provide maximum daily dose (MDD). It states in the 'Dosage and Administration Section' that one application of shampoo should be sufficient. As Identification Thresholds and Qualification Thresholds are dependent on MDD the value of MDD is calculated on the basis of single application size of 12 mL.

$$(MDD) = 12mL \times$$ ——— *

* All the quantities used in calculation are from the executed batch record.

B. Description of How the Drug Product is Intended to be Used

Topical administration for treatment of tinea (pityriasis) versicolor.

C. Basis for Approvability or Not-Approval Recommendation

CMC deficiencies
EER pending
Bio pending review

III. Administrative

A. Reviewer's Signature 7/29/04

B. Endorsement Block

HFD-620/ Suhas Patankar, Ph.D./ 7/29/04
HFD-620-/ Shing Liu, Ph.D./ S.H. Liu 7/29/04
HFD-617/ Wanda Panphile, Pharm D./ 7/29/04

C. CC Block

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of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #1

4. [redacted]

5. [redacted]

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please provide any additional long term stability data that may be available.

2. All facilities referenced in the ANDA should have a satisfactory compliance evaluation at the time of approval. We have requested an evaluation from the Office of Compliance.

3. [redacted]

4. Your bioequivalence information is pending review. Deficiencies, if any, will be communicated to you separately.

Sincerely yours,

Ahaghton for 7/29/04

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-942
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-620/S. Patankar, Ph.D./ 7/29/04
HFD-620/S.Liu, Ph.D./ S. H. Liu 7/29/04
HFD-627/W.Panphile, Pharm D./ 7/29/04

F/T by:

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TYPE OF LETTER: NOT APPROVABLE -MINOR

APPEARS THIS WAY
ON ORIGINAL

ANDA 76-942

Ketoconazole Shampoo, 2%

QLT USA, Inc.

Suhas Patankar, Ph.D.
Chemistry Division III

Table of Contents

Chemistry Review Data Sheet

1. ANDA: 76-942

2. REVIEW # : 2

3. REVIEW DATE: 8/31/2004
   Revised: 10/18/2004
   Revised: 4/4/2005

4. REVIEWER: Suhas Patankar, Ph.D.

5. PREVIOUS DOCUMENTS:

Firm	Document Date
Original ANDA Submission	December 13, 2003
Resubmission (Response to Refuse to file Letter)	February 5, 2004
Labeling Amendment	March 18, 2004
Labeling Amendment	April 5, 2004

Agency	Document Date
Agency Refuse to File Letter	January 27, 2004
Agency Acknowledgement Letter (Acceptable for filing: February 9, 2004)	February 18, 2004
Labeling Deficiency Letter	March 17, 2004
CMC Deficiency Letter	July 29, 2004

6. SUBMISSION(S) BEING REVIEWED:

Amendment (Response to CMC Deficiencies)	August 13, 2004
Minor Amendment	August 18, 2004
Minor Amendment	September 02, 2004
Amendment for Name Change	January 3, 2005
Bioequivalence Amendment	January 4, 2005
Bioequivalence Amendment	January 18, 2005

7. NAME & ADDRESS OF APPLICANT:

Chemistry Review Data Sheet

Name: QLT USA, Inc. (Atrix Laboratories, Inc.)

Address: 2579 Midpoint Drive

Fort Collins, CO 80525-4417

Representative: Cheri Jones

Telephone: (970) 212-4901

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Ketoconazole Shampoo, 2%

9. LEGAL BASIS FOR SUBMISSION:

Please see Review # 1.

10. PHARMACOL. CATEGORY: Antifungal

11. DOSAGE FORM: Shampoo

12. STRENGTH/POTENCY: 2%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: Rx

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

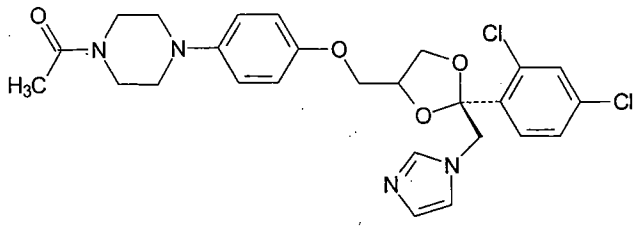
_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Formula: $C_{26}H_{28}Cl_2N_4O_4$
CAS # : 65277-42-1
Molecular Weight: 531.44

Ketoconazole. Piperazine, 1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-(1*H*-imidazole-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-, *cis*-.



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			3	Adequate	10/15/2004	Reviewed by S. Patankar
	III			4			
	III			4			
	III			4			
	III			4			
	IV			4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

Chemistry Review Data Sheet

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
ANDA	76-419	Approved 1/5/04 (Ketoconazole Shampoo 2% by Clay-Park)

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	11/17/04	D'Ambrogio, J.
Methods Validation	N/A		
Labeling	Acceptable	4/16/04	Wu, R.
Bioequivalence	Acceptable	3/28/05	Ho, S.
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt.
__X__ Yes ____ No If no, explain reason(s) below

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for ANDA 76-942

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approvable

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not applicable

II. Summary of Chemistry Assessments

A. Description of the Drug Substance(s) and Drug Product(s)

Ketoconazole, a synthetic imidazole derivative, is an azole antifungal agent. This USP drug substance is a white or almost white crystalline powder and is practically insoluble in water. Ketoconazole has pK_as of 2.9 and 6.5.

Atrix's proposed drug product, Ketoconazole Shampoo, 2%, is not an USP compendial item. Atrix's drug product is a red-orange, liquid containing the antifungal in an aqueous suspension. The inactive ingredients in this formulation are sodium laureth sulfate; disodium laureth sulfosuccinate; cocamide diethanolamide; hydrochloric acid, NF; PEG-120 methyl glucose dioleate; sodium chloride, USP; sodium hydroxide, NF; fragrance; FD&C red No. 40; and purified water, USP. Atrix uses Imidurea, NF as a ——— in their formulation. Atrix's Ketoconazole Shampoo, 2% is packaged in 4 fluid oz HDPE, tapered, oval bottle with a White 20 mm/———————, fine ribbed disc cap.

The labeling does not provide maximum daily dose (MDD). It states in the 'Dosage and Administration Section' that one application of shampoo should be sufficient. As Identification Thresholds and Qualification Thresholds are dependent on MDD the value of MDD is calculated on the basis of single application size of 12 mL.

$$(MDD) = 12mL \times$$ ——————————— *

* All the quantities used in calculation are from the executed batch record.

B. Description of How the Drug Product is Intended to be Used

Topical administration for treatment of tinea (pityriasis) versicolor.

C. Basis for Approvability or Not-Approval Recommendation

Approvable due to the following:

CMC Acceptable
EER Acceptable 11/17/04
Bio Acceptable 3/28/05

III. Administrative

A. Reviewer's Signature

4/4/05

B. Endorsement Block

4/4/05

HFD-630/ Suhas Patankar, Ph.D./
HFD-630-/ Shing Liu, Ph.D./ S.H.Liu 4/4/05
HFD-617/ Lisa Kim, Pharm D./

C. CC Block

Redacted 18 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #2

cc: ANDA 76-942
ANDA DUP
DIV FILE
Field Copy

Endorsements:

HFD-630/S. Patankar, Ph.D./ 4/4/05
HFD-630/S.Liu, Ph.D./ S.H.Liu 4/4/05
HFD-617/Lisa Kim, Pharm D./ S.Park 4/4/05

F/T by:

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TYPE OF LETTER: APPROVABLE

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-942

BIOEQUIVALENCE REVIEW

Review of a Bioequivalence Study with Clinical Endpoint

ANDA # 76-942 Ketoconazole Shampoo, 2% Atrix Laboratories, Inc.

Sarah Ho, Pharm.D.
Clinical Reviewer
Office of Generic Drugs

Date of Review: March 28, 2005
Submission dates reviewed:
December 13, 2003
February 5, 2004
January 4, 2005
January 18, 2005

Table of Contents

Clinical Review for ANDA 76-942

Executive Summary

A double-blind, randomized, multi-center, randomized, parallel-group study demonstrates that Atrix Laboratories, Inc. (Atrix's) Ketoconazole Shampoo, 2% is safe and bioequivalent to McNeil Consumer's Nizoral® Shampoo, 2%, in the treatment of Tinea (Pityriasis) Versicolor. The FDA's analyses confirm that the 90% Confidence Interval (CI) of the proportional difference in therapeutic cure rates between the test and reference products at Visit 3 (Day 31±4 days) is (-.097,+.142), which is within the bioequivalence limits of (-.20,+.20). A total of 302 patients were enrolled into the study. Based on the FDA's analyses, two hundred seventy-one (271) patients were included in the Intent-to-Treat (ITT) population, and 242 were included in the Per Protocol (PP) population.

I. Recommendation on Approval

The data submitted to ANDA 76-942, using the primary endpoint of therapeutic cure rates at Visit 3 (Day 31±4 days), demonstrate bioequivalence of Atrix's Ketoconazole Shampoo, 2% with the reference listed drug (RLD), McNeil Consumer's Nizoral® Shampoo, 2%. Therefore, the test product is recommended for approval.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Atrix's Ketoconazole Shampoo, 2% is a prescription antifungal product indicated for the treatment of tinea (pityriasis) versicolor. Atrix conducted a clinical endpoint study, enrolling 302 patients, to establish the bioequivalence of their proposed Ketoconazole Shampoo, 2% to the RLD, Nizoral® Shampoo, 2%, in the treatment of tinea (pityriasis) versicolor. All patients were randomized to receive either Atrix's proposed product (Test), Nizoral® (Reference) or placebo.

B. Comparative Efficacy

The primary endpoint of this product is therapeutic cure at Visit 3 (Day 31±4 days). The sponsor defined therapeutic cure as a negative KOH test, a score of no greater than two for either hyper or hypopigmentation and a score of zero for the Investigator Global Evaluation, desquamation/scaling, pruritus/itching and erythema.

According to the FDA's analysis, the therapeutic cure rates in the Per Protocol (PP) population at Visit 3 were 62% in the test group and 59% in the reference group. The therapeutic cure rate for the Placebo group was 15%, using the Intent-to-Treat (ITT) population. The 90% CI for proportional difference in therapeutic cure rates between the two products was (-.097,+.142), which is within the bioequivalence limits. The

therapeutic cure rates of both products were demonstrated by the FDA's analysis to be superior to placebo.

C. Comparative Safety

A total of 300 patients received medication. Of these, 128 received the Test product and 130 received the Reference product. Drug safety was monitored via questioning during visits. No deaths were reported. Only one serious adverse event, considered unrelated to the study medication, in the Reference group was reported. A total of 32 adverse events were reported during this study (12 in the Test, 17 in the Reference and 3 in the Placebo). Most commonly reported adverse events (AE) were headache (0 Test vs. 3 Reference) and sore throat (1 Test vs. 2 Reference). There were no skin related adverse events reported in the Test group. The Reference group had 2 skin related adverse events and the Placebo group had 3 skin related adverse events. The data demonstrate that the Test product is no worse than the Reference product with regard to skin irritation.

Clinical Review

I. Introduction and Background

A. Drug Product

1. Drug Established Name: Ketoconazole Shampoo, 2%
2. Drug Class: Anti-fungal

B. Reference Listed Drug (RLD)

1. RLD Name: Nizoral® Shampoo, 2% (McNeil Consumer's)
2. NDA: 19-927
3. Date of Approval: Original NDA approved on August 31, 1990. Indication for tinea (pityriasis) versicolor approved on October 10, 1997.
4. Approved Indication(s): for the treatment of tinea (pityriasis) versicolor caused by or presumed to be caused by *Pityrosporum orbiculare* (also known as *Malassezia furfur or M. orbiculare*)
5. Dose, Route of Administration and Regimens: One application of shampoo to damp skin of the affected area and a wide margin surrounding the area should be sufficient. Lather, leave in place for 5 minutes, and then rinse off with water.
6. Description of the reference drug, including pertinent safety or dosing considerations: Nizoral® (Ketoconazole) Shampoo, 2% contains the broad-spectrum synthetic antifungal agent ketoconazole in an aqueous suspension for topical use. It is indicated for the treatment of tinea (pityriasis) versicolor caused by or presumed to be caused by *Pityrosporum orbiculare* (also known as *Malassezia furfur* or *M. orbiculare*). The approved labeling directs patients to lather and leave the shampoo on the affected damp skin area for 5 minutes and then rinse off with water. One application of the shampoo should be sufficient for the approved indication. The most common adverse events reported with the topical use of

Nizoral® (Ketoconazole) Shampoo, 2% were pruritus, application site reaction, and dry skin. None of these adverse events occurred in more than 3% of the patients in the clinical trials of this product.

7. Brief Discussion about the indication

Tinea (pityriasis) versicolor is a non-contagious infection of the skin caused by *Pityrosporum orbiculare (Malassezia furfur)*. This commensal organism is part of the normal skin flora. The condition is often recurrent and may give rise to hyperpigmented or hypopigmented patches on the trunk, which may extend to the neck, arms and upper thighs. Clinical findings result from the rash that presents with small and scaly white-to-pink to tan-to-dark spots and pruritis that is more intense when a person gets hot. Tinea versicolor is common in teenagers or young adults but is rare in the elderly and children. People with oily skin are more susceptible compared to those with naturally dry skin. The appearance of tinea versicolor can be easily recognized by a dermatologist, but the diagnosis is confirmed by microscopic identification for the presence of *Pityrosporum orbiculare*.

Treatment of the infection may not immediately result in restoration of pigment to the affected sites. Normalization of pigment following successful therapy is variable and may take months, depending on individual skin type and incidental sun exposure.

C. Regulatory Background

1. INDs, Protocols, and/or Control Documents submitted by this sponsor

The study submitted in this ANDA was conducted by ———. ——— submitted a protocol ——— for this study. The Office of Generic Drugs reviewed the protocol and provided comments dated March 17, 2003.

2. INDs, Protocols, and/or Control Documents submitted by other sponsors

Doc Type	Doc Number	Sponsor	Drug Product	Status
CD	97-163	[redacted]	Ketoconazole Shampoo, 2%	Completed on 8/29/97
Bio-IND	[redacted]	[redacted]	Ketoconazole Shampoo, 2%	Completed on 9/5/01

3. Previous ANDA submissions for same or related product

ANDA	Sponsor	Drug Product	Status
76-419	Clay-Park Labs, Inc.	Ketoconazole Shampoo, 2%	Approved on 1/7/04

75-581	Teva Pharmaceuticals USA	Ketoconazole Cream, 2%	Approved on 4/25/00
75-638	Taro Pharmaceuticals USA Inc.	Ketoconazole Cream, 2%	Approved on 12/18/02
76-294	Altana Inc.	Ketoconazole Cream, 2%	Approved on 4/28/04
		Ketoconazole Suspension	Withdrawn
		Ketoconazole Cream	Withdrawn

D. Other Relevant Information
None

II. Description of Clinical Data and Sources

A. CRO: [redacted]

B. Study Period
1. First Patient Entered: April 30, 2003
2. Last Patient Completed: September 18, 2003

C. Study Centers, Investigators and Enrollment

Site Number	Investigator	Location	Number enrolled*
01	[redacted]	[redacted]	11
02			3
03			17
04			3
05			35
06			21
07			32
08			28
09			28
10			55
11			16
12			28

13			10
14			13

* Met inclusion/exclusion criteria and used the study drug (Safety Population).

III. Clinical Review Methods

A. Overview of Materials Consulted in Review

1. Original Submission:
   The original submission dated December 13, 2003 was mostly in electronic format & located in Vol. 1.1. The original submission was Refused to Receive (RTR). The sponsor submitted an amendment dated February 5, 2004 in response to the OGD's RTR letter, which was subsequently accepted for filing.

2. Study Amendments (Submitted [date]):
   Bioequivalence Amendment (Submitted January 4, 2005)
   Bioequivalence Amendment (Submitted January 18, 2005)

3. Medical Officer Review of NDA#/ANDA#:
   Medical Officer Review of NDA 19-927/S-012 (Phyllis Huene, M.D., HFD-540)
   Medical Review of ANDA 76-419 (Carol Kim, Pharm.D., HFD-600)

B. Overview of Methods Used to Evaluate Data Quality and Integrity

Division of Scientific Investigations Report:

Four of the 14 clinical investigation sites had already been inspected in association with other ANDAs [redacted]. Two of these four sites enrolled the greatest number of patients for this ANDA (76-942), both enrolling ≥35 patients. The other two sites enrolled 28 and 17 patients. The DSI reports for the four ANDAs were dated August 2003, July 2003, July 2001 and May 2001, respectively. Three of the sites inspected received deficiencies which were categorized as VAI (voluntary action indicated) and three of the sites also received Form 483 during these previous investigations. Review of this sponsor's data did not raise concerns about data quality and integrity. Therefore, an inspection of the clinical sites for this ANDA was not necessary.

C. Were Trials Conducted in Accordance with Accepted Ethical Standards

The sponsor reported that the study was conducted according to the Code of Federal Regulations Guidelines for Good Clinical Practice (Code of Federal Regulations (21 CFR), Parts 50, 54, 56, 312 and 314), the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice (ICH Guideline E6) and the Declaration of Helsinki on the ethical conduct of medical research (Edinburgh, Scotland, 2002).

Prior to study initiation the protocol and the informed consent form were reviewed and approved for all investigators by the ——— Independent Institutional Review Board —IIRB). The—IIRB acted as a central IRB for this study.

D. Evaluation of Financial Disclosure

The sponsor certified that all the investigators involved in this study did not have any financial arrangements, significant payments, proprietary interest or equity interest to report.

IV. Review of Bioequivalence

A. Brief Statement of Conclusions

The sponsor's study supports the bioequivalence of the test product with the reference product.

B. General Approach to Review of the Comparative Efficacy of the Drug

The sponsor conducted one clinical study. The sponsor's study, entitled "A Randomized, Double-Blind, Placebo Controlled, Parallel Design, Multiple-Site Study to Evaluate the Clinical Equivalence of Two Ketoconazole 2% Shampoos in Patients with Tinea (Pityriasis) Versicolor," was reviewed to evaluate the comparative efficacy and safety of the proposed drug. The ANDA was submitted largely as an Electronic document. Thus, the electronic submissions of the ANDA as well as the paper submission were reviewed in detail.

C. Detailed Review of Bioequivalence Studies with Clinical Endpoints

1. **Protocol Number**: 70236209

2. **Title**: A Randomized, Double-Blind, Placebo Controlled, Parallel Design, Multiple-Site Study to Evaluate the Clinical Equivalence of Two Ketoconazole 2% Shampoos in Patients with Tinea (Pityriasis) Versicolor.

3. **Objective:**
   a. The primary objective of this study was to evaluate the efficacy and safety of the test formulation of ketoconazole shampoo, 2% as compared to the already marketed formulation Nizoral® (ketoconazole) Shampoo, 2% (manufactured by McNeil Consumer Products) in patients with tinea (pityriasis) versicolor.
   b. In addition, the efficacy of both the test and reference shampoos was compared to a placebo shampoo.

4. **Study Design:** A randomized, double-blind, placebo controlled, parallel design, multiple-site, clinical study with 300 male and non-pregnant female patients aged eighteen (18) years or older, with confirmed tinea versicolor, was conducted to evaluate the bioequivalence of two formulations of ketoconazole shampoo, 2%.

Study participants who met the inclusion/exclusion criteria for the study were randomly assigned in a 3:3:1 ratio (Test:Reference:Placebo) to one of the three treatment groups. Study participants were required to use the shampoo on a single occasion according to the instructions provided to them.

On Days 0 (Baseline), 10 and 31, KOH tests were obtained and the Investigators made complete assessments of the severity of signs and symptoms and provided an overall Investigator rating of the infection. In addition, at all visits patients were questioned about any adverse events, concomitant medication use and their compliance with the protocol requirements.

Reviewer's comments: *In another section of the sponsor's study report, the baseline visit is referred to as Day 1. The baseline visit should be noted as Day 0. The day of study medication application would be considered Day 1. The FDA statistician is requested to recalculate the visit window for Visit 2 and Visit 3 using the application date as Day 1.*

Primary determination of clinical equivalence was determined by comparing the overall cure (negative mycological and clinical cure) at the final visit (Day 31) between the test and reference formulation groups. Overall cure, mycological cure and Investigator assessment ratings at Day 10 and Day 31 were used as supportive data as appropriate. The overall cure rate for both active treatment groups was also compared to the placebo group for validation purposes.

a. Treatments
   i. **Test**: Ketoconazole Shampoo, 2% (Atrix Laboratories, Inc.) Lot Number: 1646 Manuf: 2/4/03
   ii. **Reference**: Nizoral® (ketoconazole) Shampoo, 2% (McNeil Consumer Products) Lot Number: 02FL076 Exp: 6/2004
   iii. **Placebo**: Shampoo base only (Atrix Laboratories, Inc.) Lot Number: 1647 Manuf: 1/27/03

b. Drug Administration

   A single topical application for all three products. All patients were provided with the following written instructions on how to use the shampoo: "After wetting the infected areas apply the complete contents of the shampoo bottle and then lather the whole torso and scalp, arms to elbows, and lower body including groin area and legs to knees with the shampoo. Allow the shampoo lather to sit on the skin for at least five minutes before rinsing off with water".

   Each patient was required to use the shampoo as instructed on a single occasion within three days of their baseline visit. This single use dosing regimen was chosen as it is the recommended dosing regimen for the reference product Nizoral®.

c. Study Population

i. Inclusion Criteria

(a) Male or non-pregnant, non lactating females 18 years of age or older.

(b) Signed informed consent form

(c) If female and of child bearing potential, have a negative urine pregnancy test at the baseline visit and prepare to abstain from sexual intercourse or use a reliable method of contraception during the study.

(d) The presence of infection confirmed by the observation of a positive KOH test for the presence of *Pityrosporum orbiculare*.

(e) Clinical signs and symptoms of tinea versicolor as defined by a combined severity score of at least 4, with at least one of the following signs or symptoms rated at least 2 using the following scale; desquamation/scaling, pruritus/itching, erythema, hyperpigmentation, hypopigmentation. 0=absent, 1=mild, 2=moderate, 3=severe (see Endpoints for severity definitions).

Reviewer's comment:

- *The inclusion criteria as outlined by the sponsor is appropriate for this study.*
- *All enrolled patients had a positive KOH.*
- *All patients had a combined severity score of at least 4.*
- *All except for two patients (08/1070 and 07/1186, both in the safety population) had at least one of the signs or symptoms rated with a score of at least 2.*

ii. Exclusion Criteria

(a) Use of any systemic or topical antifungals, corticosteroids or immunosuppressive drugs within 30 days of the baseline visit.

(b) Use of any prescription or OTC topical antifungal, antipruritus, corticosteroid, selenium sulfide or zinc pyrithione preparations within 14 days of the baseline visit.

(c) Any known hypersensitivity to ketoconazole or other imidazole antifungals or other shampoos, soaps or cosmetics.

(d) Females who are pregnant, lactating or likely to become pregnant during the study.

(e) Significant history or current evidence of chronic infectious disease, system disorder, organ disorder or other medical condition that in the Investigator's opinion would place the study patient at undue risk by participation or could jeopardize the integrity of the study evaluations.

(f) Evidence of any concurrent fungal infection including oral, vaginal or chronic mucocutaneous candidiasis, systemic fungal infection or dermatophyte infection.

(g) Treatment for tinea versicolor within the past six months that has been unresponsive to prescription topical or oral antifungals.

(h) Receipt of any drug as part of a research study within 30 days prior to dosing.

Reviewer's comment:

- *The sponsor has appropriately incorporated the comments provided by OGD regarding the exclusion criteria .*
- *The sponsor listed topical antifungals and corticosteroids with differing washout periods. The washout period should be 14 days.*

d. Procedures/Observations

i. Visit 1 (Screening Visit) - Prior to being enrolled into the study all patients underwent a comprehensive screening procedure (see Table 1 below for details). If patients met the inclusion/exclusion criteria they were randomized to the next study number and dispensed the study drug along with written instructions on dosing procedures and how to complete the instruction sheet. All patients were also provided with Dove® Sensitive Skin Soap to use during the study and instructions on protocol restricted medication use during the study. The date of their second visit (Day 10) was scheduled.

ii. Follow-up visits (Visits 2 and 3) - See Table 1 for details.

iii. Medication use - Each patient was required to use the shampoo as instructed on a single occasion within three days of their baseline visit. This single use dosing regimen was chosen as it is the recommended dosing regimen for the RLD, Nizoral®.

Table 1: Study Schematic (per sponsor)

	VISIT 1 Screening Visit Day 1*	VISIT 2 End of treatment Day 10 (±4 days)	VISIT 3 End of Study Day 31 (±4 days)
Informed Consent	X		
Demographics	X		
Medical History	X		
Pregnancy Test	X		
Investigator Global Assessment	X	X	X
Signs and Symptoms	X	X	X
KOH Stain	X	X	X
Dispense Study Medication	X		
Return Study Medication		X	
Adverse Events		X	X
Concomitant Medications	X	X	X
Study Discharge			X

* ***Reviewer's comment****: Visit 1 should be considered Day 0. The day of study medication application should be designated as Day 1.*

iv. Restrictions - The following concomitant medications were restricted while enrolled in the study.
(a) Any topical antifungal or antimycotic agents
(b) Any systemic antifungals
(c) Prescription or OTC medicated shampoos or soaps during the study. All patients were provided with a mild cleansing soap (Dove® Sensitive Skin) for use during the study. Patients were instructed not to use any medicated shampoos during the study (e.g. Head and Shoulders®, T-Gel® or equivalent).
(d) Oral antibiotic use prior to or during the study was allowable unless the investigator considered that the patient should be excluded for medical/safety reasons.

Reviewer's comments:

- *The sponsor's restrictions are appropriate for the study of this proposed product.*
- *Systemic or topical corticosteroids should be a prohibited concomitant medication during the study period. (One patient used systemic corticosteroid during the study.)*

e. Safety measures
i. Patients who, when discontinued from the study, had unresolved adverse events were followed up, where possible, by telephone and certified letter to confirm the outcome of the event. At each visit patients were questioned about any adverse events or concomitant medication use. The event, start and stop date, outcome, severity, relationship to study drug and any concomitant medication use were reviewed and evaluated by the Investigator for each event. Adverse events were coded into MEDRA terminology at the time of data entry.

f. Reasons for Discontinuation of Patients
Patients were discontinued from further participation for the following reasons:
i. Failed to be compliant with the dosing requirements of the study, in that they failed to use the study medication within three days of their baseline assessments.
ii. Withdrew consent to continued participation in the study.
iii. Required use of prohibited concomitant medication for concurrent illness.
iv. Developed concurrent illness or worsening of tinea versicolor, that the investigator considered it in the patient's best interest to discontinue study participation.
v. Failed to return for study visits on a timely basis.

Reviewer's comments:

- *If a patient discontinued due to worsening of tinea versicolor then that patient should be included in the PP population as a treatment failure.*
- *Patients who were discontinued from the study early because of a treatment-related adverse event should be excluded from the PP population.*

g. Efficacy Measurements & Severity Scales

i. Four efficacy measurements were evaluated in this study: clinical cure, mycological cure (negative KOH), Investigator Global Evaluation and signs and symptoms.

(a) **Investigator Global Evaluation Scale** (overall severity of the infection)
0= no scaling, itching or erythema
1= mild scaling, limited distribution, with or without itching and with or without erythema
2= moderate scaling, with or without itching
3= severe, extensive distribution of scaling, with or without itching.

(b) **Individual Signs and Symptoms Severity Scales**
Desquamation/Scaling
0 = Absent (no sign of dryness or scaling)
1 = Mild (slight but definite roughness; fine scaling present)
2 = Moderate (moderate roughness; somewhat coarse scaling, some cracking may be present)
3 = Severe (marked roughness; course scaling; cracking evident)

Pruritus/Itching
0 = Absent (none)
1 = Mild (slight itching: not really bothersome)
2 = Moderate (definite itching; somewhat bothersome; without loss of sleep)
3 = Severe (intense itching that has caused pronounced discomfort; night rest interrupted. Excoriations of skin from scratching may be present)

Erythema
0 = Absent (none)
1 = Mild (light red/pink)
2 = Moderate (red but still not dark)
3 = Severe (very red or dark)

Hyperpigmetation
0 = Absent (none)
1 = Mild (slight or indistinct areas of darker skin compared to normal skin tone)
2 = Moderate (discernible areas of darker skin compared to normal skin tone)
3 = Severe (areas of intense dark skin tone with very discernible borders compared to normal skin
tone).

Hypopigmetation
0 = Absent (none)
1 = Mild (slight or indistinct areas of lighter skin compared to normal skin tone)
2 = Moderate (discernible areas of lighter skin compared to normal skin tone)
3 = Severe (areas of intense light skin tone with very discernible borders compared to normal skin tone).

Both the IGE and individual signs and symptom rating scales were static rating scales and required the Investigator to perform the ratings blinded at the time of the evaluation, without reference to previous ratings for that particular patient.

ii. Primary Efficacy Endpoints: The primary statistical analysis to determine bioequivalence by the sponsor was the Overall Cure Rate or "clinical cure" at Visit 3 (Day 27-35) using data from those patients who completed the study according to the protocol (the Per Protocol (PP) Population). Comparison of the superiority of the Test and Reference shampoos against Placebo was tested using the Intent-to-Treat (ITT) Population.

A patient was considered **Overall Cured** or "clinically cured" by the sponsor if the patient met all of the following criteria:
(a) had a negative KOH test
(b) were considered healed (no scaling, itching or erythema) on the Investigator Global Evaluation
(c) had a zero score (absence) for desquamation/scaling and pruritus/itching and erythema for clinical signs and symptoms and
(d) a score no greater than two (moderate) for either hyper or hypopigmetation.

Any patient who has a positive KOH test or did not meet the above criteria with respect to IGE or clinical signs or symptoms was considered a treatment failure.

Reviewer's comments:

- *The sponsor interchanged two terminologies (overall cure and clinical cure) in defining the primary efficacy endpoint. In the Synopsis section of their Study Report, the sponsor defined the primary efficacy endpoint using the term "Overall Cure Rate." In Section 9.5.2 (Primary Efficacy Variables), the sponsor used the term "Clinical Cure." In both cases, the detailed criteria to be considered "Cure" was the same. The sponsor's detailed criteria for "cure" is appropriate and is consistent with OGD's terminology for "Therapeutic Success." FDA's usual primary endpoint is "Therapeutic Success" at Visit 3.*
- *The FDA Statistician is asked to verify the sponsor's determination of therapeutic outcome and appropriately categorize each patient as therapeutic success or failure using the above described criteria.*

iii. Secondary Efficacy Endpoints: Cure rate at Visit 2 using the modified Per Protocol (mPP) Population and mycological cure, Investigator's Global Evaluation (IGE) and individual signs and symptoms at Visit 2 and Visit 3 using the PP population.

Reviewer's comments:

- *The results of the secondary endpoints would only be supportive. At this time, the FDA statistician is not asked to analyze the secondary endpoints.*

h. Statistical analysis plan

i. Determination of baseline comparability of all three treatment groups using all patients dosed was planned to be compared by the sponsor using appropriate statistical tests (e.g., Scheffes Paired Comparison Test, Cochran-Mantel-Haenszel Test).

ii. No interim analysis was planned during the study nor was any conducted.

iii. **Patient Demographics** – The groups were to be compared for basic demographics (gender, age and race) and IGE. Significance levels would be adjusted for experiment-wise error rate.

iv. **Bioequivalence** - Bioequvalence was to be determined using the PP population only. Determination of bioequivalence was set *a priori* both by the protocol and using current OGD/FDA criteria. Bioequivalence was to be concluded if the 90% confidence interval (CI) of the difference between the Test and Reference in the proportion of patients with a clinical cure at Visit 3 fell within the established bioequivalence limits of (-.20, +.20).

v. **Efficacy** - Using the ITT population, both the Test and Reference treatment groups would be considered to be superior to the Placebo treatment group if at Visit 3 (or second visit carried forward, if the patient did not complete the study) the primary efficacy variable of clinical cure was superior to the Placebo group using a pre-determined level of significance of $p<0.05$.

vi. **Per-Protocol Population** – For the primary analysis of bioequivalence, the PP population was utilized. According to the sponsor, the PP population comprised of participants who:
(a) completed the final study visit (End of Study, Visit 3) within Day 27 to Day 35 after starting treatment,
(b) were compliant with the dosing procedures of the study and
(c) did not use any restricted medications during the study.

Reviewer's comment:

- *To be included into the PP population, the patient should also have met inclusion and exclusion criteria. Thus, the PP population should include those patients who:*
  - *met inclusion and exclusion criteria,*
  - *used the medication within 3 days of the baseline visit*
  - *returned for Visit 3 (unless terminated early due to treatment failure) and*
  - *was compliant with the protocol restrictions*
- *As mentioned above, patients who discontinued early due to an adverse event should be excluded from the PP population.*
- *LOCF should only be used for patient who failed to return for Visit 3 or who discontinued early from the study due to treatment failure. LOCF of Visit 2 should NOT be used for patients who used prohibited medications between Visits 2 and 3 in the PP population.*

vii. **Modified Per-Protocol Population** – For analysis of clinical cure at Visit 2 the mPP population was used. The mPP population included all patients who completed the study, according to the protocol, up to and including Visit 2.

Reviewer's comments: *For the purposes of FDA's analysis, there is no need to define a mPP population.*

viii. **Intent-to-Treat Population** – For determination of the relative efficacy of the Test and Reference formulations compared to placebo, the ITT population was used. The sponsor defined this population to include:
(a) all patients included in the PP population, plus
(b) all those patients who completed a second visit and
(c) were compliant with the protocol restrictions to that point.
(d) For those patients who failed to return for Visit 3 or used prohibited medications between Visits 2 and 3, or who where discontinued from further participation for some other reason, their second visit (Visit 2) data was carried forward (LOCF) and used in this analysis of efficacy.

Reviewer's comment:

- *The ITT population should include patients who:*
  - *met inclusion and exclusion criteria,*

- *used the medication and*
- *returned for at least one follow-up visit.*

- *Patients should NOT be excluded from the ITT population for protocol violations.*

ix. **Safety** - Comparison of adverse events between the three treatment groups. All patients who used at least one of the three study treatments were to be included in the adverse event/safety profile analysis. Data would be analyzed using descriptive analysis and if sufficient data was generated, Chi-square testing would be performed.

5. Study Conduct

a. Compliance

Each patient was provided with an instruction sheet to record the date of shampoo application. At Visit 2, patients were required to return their used bottle of shampoo and confirm the date that they used the shampoo. Patients who failed to report using the study drug within three days of their baseline visit were dropped from the study by the investigator and end of study procedures completed. Two patients failed to use any of the shampoo at all and were dropped from the study by the relevant investigator with no study follow up testing performed. As these patients did not actively participate in the study, no data is included for these patients. Patients 08/1043, 08/1045, 08/1047, 08/1048, 08/1065, 12/1145, 12/1149 and 12/1150 did not use their study medication within 3 days of the baseline visit. These eight patients were included in the safety analysis only.

b. Randomization

Study participants who met the inclusion/exclusion criteria for the study were randomly assigned in a 3:3:1 ratio (Test:Reference:Placebo) to one of the three treatment groups. The randomization was generated in blocks of 7 and patients were allocated to treatment in sequential order as they entered the study. The randomization was generated and held by the Biostatistics department of Atrix Laboratories, Inc. using SAS Version 8 software. It was not sent to the statisticians until after the last patient had completed the study and the database had been locked. No interim analysis was performed during the study.

Reviewer's comment: *The sponsor should be advised that for a blinded study, the study drug assignment should be provided in a sealed code for use by FDA. The sealed code should be maintained at each testing facility. Please refer to "Handling and Retention of BA and BE Testing Samples", posted May, 2004 for details.*

c. Blinding

i. The Test and Placebo shampoos were manufactured by Atrix Laboratories, Inc. The Placebo formulation was identical to the test product with the exception that it contained no ketoconazole. The Reference product was a commercial lot of Nizoral® purchased and provided by the Study Sponsor.

The Test, Reference and Placebo shampoos were identical in appearance. All three were red to orange-red, clear flowing shampoos and were provided in identical looking bottles. All three bottles had identical labeling and were provided in plain white sealed boxes to the patient.

ii. Each bottle of study drug was presented to the patient in a sealed plain white box. A two part blinded label was attached to the study box containing the shampoo. At the time of drug dispensing the label was completed with patients' initials and date of dispensing. One part of the study label was retained at the study site as part of the source records. The second part of the label remained on the box of shampoo. The study drug label retained at the study site had a scratch off covering that could be removed in case of medical emergency. The study blind was not broken for any of the patients in the study.

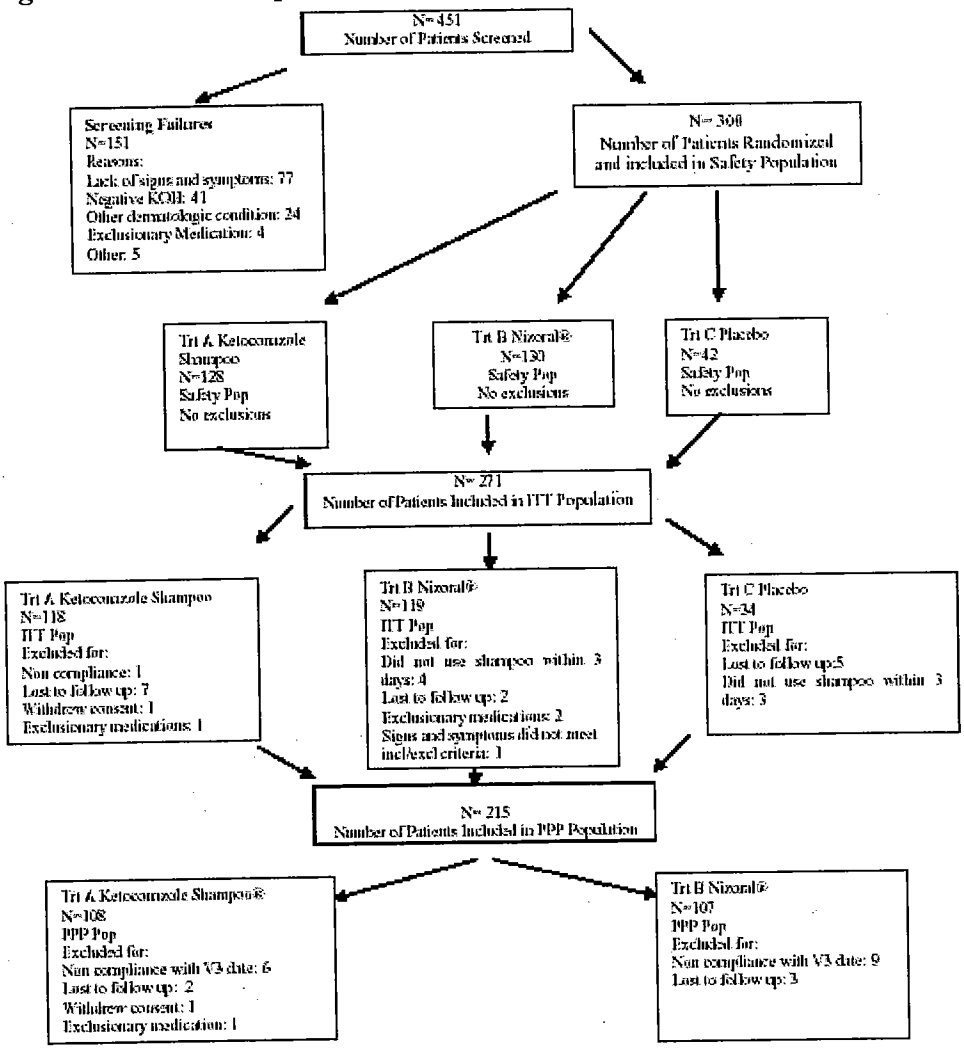
d. Reserve Samples

Each site was required to pick one block of study drug at random from all shipments of study drug sent to them as retention drug samples. The block was picked prior to the first patient being enrolled at the site and if the site received any additional study drug shipments, an additional block was picked from each shipment. Each investigative site signed a statement confirming they would retain these drug supplies according to 21 CFR 320.38 and 320.63. Monitoring visits to each of the sites confirmed that retention samples had been randomly picked at each site. Unused bottles of shampoo and retention samples were retained at the study site.

e. Study Population

Four hundred and fifty-one (451) patients were screened for study participation and 302 patients were enrolled into the study in 14 sites. Two patients returned the study drug without ever using it and were considered not to have actively participated. Of the 300 patients who used study drug, 128 patients were randomized to the test product, 130 were randomized to the reference product and 42 were randomized to the placebo treatment group. Figure 1 provides a summary of the patient disposition in the treatment groups according to the sponsor.

Figure 1: Patient Disposition (per sponsor)



f. Safety Population (per sponsor)
Three hundred (300) patients used one of the three study drugs on at least one occasion and all of these patients were included in the safety analysis.

g. ITT population (per sponsor)
Two hundred and seventy-one (271) patients were included in the ITT analysis, 118 in the Test product, 119 in the Reference product and 34 in the Placebo groups.

h. mPP Population (per sponsor)
Two hundred and thirty-four (234) patients were included in the mPP population, 116 in the Test group and 118 in the Reference.

i. PP Population (per sponsor)
Two hundred and fifteen (215) patients were included in the PP population, 108 in the Test product and 107 in the Reference product group.

j. Protocol Deviations (per sponsor)
302 patients were dispensed study drugs.

i. Two patients did not use the shampoo at all.
ii. Several patients were included in the study despite not meeting the inclusion/exclusion criteria. These patients along with their treatment group designation were as follows:
   (a) 01/1225 (PP), 04/1465 (PP), 07/1185 (PP), 07/1186 (Safety), 07/1195 (PP), 12/1143 (PP) and 13/1361 (PP) did not have a urine pregnancy test conducted prior to being included in the study. With exception of one patient (07/1195 who was given a pregnancy test at her second visit that was negative), all of these female patients were of non-child bearing potential.
   (b) 07/1186 (Safety) and 08/1070 (Safety) did not have at least one sign or symptom that scored at least a two at baseline.
   (c) 06/1133 (Safety) and 10/1390 (Safety) used nasal corticosteroids prior to and/or during the study.
   (d) 09/1033 (PP) did not meet wash-out period for prior anti-fungal treatment by one day (last use 29 days prior to baseline visit).
iii. Three patients, 03/1444 (ITT, as late for final visit), 09/1002 (ITT, dropped at Visit 2) and 10/1408 (PP) used other topical medications (anti-biotic acne-treatments) on their face during the study.
iv. Several patients were outside of the 4 day window specified for one or more of the study visits. If a patient was outside of the window for Visit 2, but was within the window for Visit 3, they were included in the PP analysis as primary determination of bioequivalence was based on Visit 3 data. If a patient made a second visit and was compliant with the protocol up to that point, but either did not make Visit 3, or was outside of the window for Visit 3 (Day 27 to Day 35) they were excluded from the PP analysis but included in the ITT analysis. The mPP included all patients who made Visit 2 within the specified window and without protocol deviations up to that point.
v. Patients who took prohibited concomitant medications during the study were dropped by the investigator from further participation. If they completed a second visit prior to their deviating from the protocol, the second visit data was carried forward (LOCF) and they were included in the ITT analysis as appropriate.

Reviewer's Comments:

- *The following patients should be excluded from the PP population:*
  - *09/1033 for not meeting the wash-out period for prior topical anti-fungal treatment (clotrimazole) for tinea versicolor.*
  - *03/1429 for use of a systemic corticosteroid (methylprednisolone) during the study.*
- *The following patients should be excluded from the ITT population:*
  - *09/1033 for not meeting the wash-out period for prior anti-fungal treatment for tinea versicolor.*

k. Baseline Patient Characteristics (per sponsor)
The following parameters were used to evaluate comparability of the baseline characteristics of the three treatment groups; age, gender, race and Investigator Rating Scale. Summary data by treatment group is provided in Table 2.

i. **Age:** The patients enrolled in the study were aged from 18 to 76 years with the mean age being 35.6, 36.3 and 39.9 years in the Test, Reference and Placebo groups, respectively. Difference among the groups was evaluated using SAS PROG GLM with Scheffe's paired comparison test among treatment groups. There was no statistical difference among treatments ($p=0.2398$) nor for any paired comparison ($p>0.05$).

ii. **Gender:** Of the 300 patients dosed, 174 were female and 126 were male. Difference among the groups was tested using SAS PROC FREQ. There was no statistical difference among the three treatment groups for gender distribution ($p=0.9769$, Cochran-Mantel-Haenszel).

iii. **Race:** The patient population consisted of 209 Caucasians, 61 Hispanics, 23 African Americans, 2 Asians and 5 patients of Other racial origin. Difference between the groups was tested using SAS PROC FREQ. There was no statistical difference among the three treatment groups in racial mix ($p=0.4546$, Cochran-Mantel-Haenszel)

iv. **Investigator Global Rating:** Of the 300 patients dosed the mean Investigator Global Rating score at baseline for the Test, Reference and Placebo groups were 2.04, 2.02 and 1.90, respectively. Difference among the groups was tested using SAS PROC GLM with Scheffe's paired comparison test between treatment groups ($p=0.4549$). There was no statistical difference among the three treatment groups ($p=0.4549$) nor for any paired comparison ($p>0.05$).

v. **Baseline comparability:** As there was no statistically significant difference for any of the baseline parameters all other statistical procedures were conducted without need for treatment group baseline correction.

Table 2: Baseline Characteristics (per sponsor)

	Test	Reference	Placebo
Age in years (mean ± SD)	35.6 ± 14.6	36.3 ± 14.6	39.9 ± 13.4
Gender (number, %)			
Male	54(42%)	55(42%)	17(40%)
Female	74(58%)	75(58%)	25(60%)
Race (number, %)			
African American	8 (6%)	14 (11%)	1 (2%)
Asian	2 (2%)	0 (0%)	0 (0%)
Caucasian	88(69%)	89 (68%)	32 (76%)
Hispanic	26(20%)	27 (21%)	8 (19%)
Other	4 (3%)	0 (0%)	1 (2%)
Investigators Global Rating			
Score (mean ± SD)	2.04 ± 0.62	2.02 ± 0.60	1.90 ± 0.62

6. Results

a. Bioequivalence (per sponsor)

The percentage cure rate in the Test group was 62.04% and 58.88% for the Reference group (Table 3). The 90% confidence interval for the difference was (-.1444, +.0798), within (-.20, +.20) and thus demonstrating bioequivalence.

Table 3: Bioequivalence of Per-Protocol Population at Visit 3 (per sponsor)

Cure Rate (%)		Difference Between Treatments		
			90% Confidence Interval	
Ketoconazole Shampoo	Nizoral Shampoo	Difference	Lower Limit	Upper Limit
62.04	58.88	-3.23	-14.44	7.98

b. Efficacy (per sponsor)

Using the ITT population, the cure rate for the test, reference and placebo treatment groups were 58.74%, 57.14% and 14.71%, respectively (Table 4). Both the Test and Reference products were shown to be highly significantly superior to placebo ($p<0.0001$ in both cases).

Table 4: Superiority of Test and Reference vs. Placebo in the Intent-To-Treat Population at Visit 3 (per Sponsor)

Cure Rate (%)			p-value*	
Test	Reference	Placebo	Test vs. Placebo	Reference vs. Placebo
58.47	57.14	14.71	<.0001	<.0001

*p-value for Mantel-Haenszel Chi-Square

D. Bioequivalence Conclusion

Based on the FDA's statistical analyses, the study demonstrates that the 90% CI for the proportional difference in the Therapeutic Cure rates between the Test and the Reference products at Visit 3 (Day 31) is within (-.20, +.20). A patient was considered a Therapeutic Cure by the FDA if the patient had a negative KOH test, was considered healed (no scaling, itching or erythema) on the Investigator Global Evaluation, had a zero score (absence) for desquamation/scaling and pruritus/itching and erythema for clinical signs and symptoms and a score no greater than two (moderate) for either hyper or hypopigmentation.

Reviewer's Comment: *Because the sponsor inappropriately included/excluded some patients from the PP population analysis, the FDA statistician is consulted for reanalysis and verification of the sponsor's data.*

V. Comparative Review of Safety

A. Brief Statement of Conclusions

The sponsor's data demonstrate that the Test product is no worse than the Reference product with regard to skin irritation.

B. Description of Adverse Events

All 300 patients who received the study drug were included in the adverse event analysis. A total of thirty-two (32) adverse events were reported (12 in the Test group, 17 in the Reference group and 3 in the Placebo group). Only four adverse events were considered "possibly" or "probably" drug related, one incident of mild dysgeusia in the Test group, one episode of mild pruritis in the Reference group and a mild skin burning sensation and moderate pruritus in the Placebo group.

Because of the low incidence of reported adverse events no statistical analysis was performed by the sponsor.

The sponsor concluded that there was no difference between the Test, Reference or Placebo formulations in terms of safety.

Reviewer's comments:

- *Patients in the Test group experienced less AEs than those in the Reference group (Table 5).*
- *Most commonly reported adverse events (AE) were headache (0 Test vs. 3 Reference) and sore throat (1 Test vs. 2 Reference).*
- *There were a total of 5 skin and appendages related AE reported during the study. Two (pruritus and dry skin) reported in the Reference group and three (pruritus, dry skin and burning) in the Placebo group. There were no skin and appendages related AE reported in the Test group.*
- *The only severe AE reported by the sponsor was pylonephritis (patient 10/1386) in the reference group. It was considered to be unrelated to the study medication and*

the patient recovered from the AE with the use of concomitant medications (ciprofloxacin, cefazolin, gentamicin and ceftriaxone).

- *No deaths were reported by the sponsor during this study.*
- *These data show that the Test product is no worse than the Reference product with regard to skin irritation.*

Table 5: Summary of Adverse Events (per reviewer)

	Test N=128		***Reference N=130***		***Placebo N=42***		***Total N=300***	
	Patients	***AEs***	***Patients***	***AEs***	***Patients***	***AEs***	***Patients***	***AEs***
Total Adverse Event	***8 (6.3%)***	***12***	***11 (8.5%)***	***17***	***2 (4.8%)***	***3***	***21 (7.0%)***	***32***
Related[1] AE	*1 (0.8%)*	*1*	*1 (0.8%)*	*1*	*2 (4.8%)*	*2*	*4 (1.3%)*	*4*
Severe AE	*0 (0.0%)*	*0*	*1 (0.8%)*	*1*	*0 (0.0%)*	*0*	*1 (0.3%)*	*1*
AEs causing termination[2]	*0 (0.0%)*	*0*	*0 (0.0%)*	*0*	*0 (0.0%)*	*0*	*0 (0.0%)*	*0*
AEs leading to death	*0 (0.0%)*	*0*	*0 (0.0%)*	*0*	*0 (0.0%)*	*0*	*0 (0.0%)*	*0*
Skin and Appendages AE	***0 (0.0%)***	***0***	***2 (1.5%)***	***2***	***2 (4.8%)***	***3***	***4 (1.3%)***	***5***
Related[1] AE	*0 (0.0%)*	*0*	*1 (0.8%)*	*1*	*2 (4.8%)*	*2*	*3 (1.0%)*	*3*
Pruritus	*0 (0.0%)*	*0*	*1 (0.8%)*	*1*	*1 (2.4%)*	*1*	*2 (0.7%)*	*2*
Dry Skin	*0 (0.0%)*	*0*	*1 (0.8%)*	*1*	*1 (2.4%)*	*1*	*2 (0.7%)*	*2*
Burning	*0 (0.0%)*	*0*	*0 (0.0%)*	*0*	*1 (2.4%)*	*1*	*1 (0.3%)*	*1*
Headache	***0 (0.0%)***	***0***	***2 (1.5%)***	***3***	***0 (0.0%)***	***0***	***2 (0.7%)***	***3***
Related[1] AE	*0 (0.0%)*	*0*	*0 (0.0%)*	*0*	*0 (0.0%)*	*0*	*0 (0.0%)*	*0*
Sore Throat	***1 (0.8%)***	***1***	***2 (1.5%)***	***2***	***0 (0.0%)***	***0***	***3 (1.0%)***	***3***
Related[1] AE	*0 (0.0%)*	*0*	*0 (0.0%)*	*0*	*0 (0.0%)*	*0*	*0 (0.0%)*	*0*

[1] *AEs with probable or possible relationship to study medication*

[2] *These AEs include discontinuation or interruption of the study medication*

VI. Relevant Findings From Division of Scientific Investigations, Statistics and/or Other Consultant Reviews

A. Division of Scientific Investigations

Four of the 14 clinical investigation sites had already been inspected in association with other ANDAs [redacted]. Two of these four sites enrolled the greatest number of patients for this ANDA (76-942), both enrolling ≥35 patients. The other two sites enrolled 28 and 17 patients. The DSI report for the four ANDAs were dated August 2003, July 2003, July 2001 and May 2001, respectively. Three of the sites inspected received deficiencies which were categorized as VAI (voluntary action indicated) and three of the sites also received Form 483 during these previous investigations. Review of this sponsor's data did not raise concerns about data quality and integrity. Therefore, an inspection of the clinical sites for this ANDA was not necessary.

B. Statistics

The FDA statistical analyses support the bioequivalence of the Test and the Reference products. The analyses showed that the 90% CI of the proportional difference in Therapeutic Cure rates between the Test and the Reference products at Visit 3 (Day 31) for the PP population is (-.097, .142), which is within the bioequivalence limits of (-.20, +.20). The Test and the Reference products also demonstrated superiority ($p<0.05$) over the Placebo in the ITT population for Therapeutic Cure at the Visit 3 (Day 31) endpoint ($p<0.001$).

VII. Formulation

Component	Test (% w/w)	Reference* (Quantity %)
Ketoconazole USP	2.0	2
PEG-120 Methyl Glucose Dioleate		
Hydrochloric Acid NF		
Imidurea, NF		
FD&C Red #40		
Sodium Laureth Sulfate		
Fragrance		--
Perfume Bouquet	--	
Disodium Laureth Sulfosuccinate		
Cocamide Diethanolamide		
Sodium Hydroxide NF		
Sodium Chloride USP		
Laurdimonium Hydrolyzed Animal Collagen	--	
Purified Water USP		QS

* Obtained from COMIS NDA 19-927.

[ ]

*** quantity sufficient (q.s.)

Reviewer's comment: *These qualitative and quantitative differences are acceptable at the levels listed from a regulatory perspective, as determined by the filing review from the Regulatory Support Branch.*

VIII. Conclusion and Recommendation

A. Conclusion

The data presented in this ANDA , using the preferred primary endpoint of Therapeutic Cure rates at Visit 3 (Day 31), demonstrate that Atrix Laboratories, Inc.'s Ketoconazole Shampoo, 2% is bioequivalent to the reference listed drug Nizoral® Shampoo, 2%.

B. Recommendation

This application is recommended for approval from a clinical bioequivalence standpoint.

Sarah Ho, Pharm.D.
Clinical Reviewer
Office of Generic Drugs

3/28/05
Date

Dena R. Hixon, M.D.
Associate Director for Medical Affairs
Office of Generic Drugs

3/28/05
Date

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

3/28/05
Date

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:76-942 APPLICANT: Atrix Laboratories, Inc.

DRUG PRODUCT: Ketoconazole Shampoo, 2%

The Division of Bioequivalence has completed its review and has no further questions at this time.

The data submitted to ANDA 76-942 demonstrate bioequivalence of Atrix Laboratories, Inc.'s Ketoconazole Shampoo, 2% with the reference listed drug, Nizoral® Shampoo, 2%, using the primary endpoint of Therapeutic Cure rate at Visit (Day 31).

In future applications, for a blinded study, the study drug assignment should be provided in a sealed code for use by FDA. The sealed code should be maintained at each testing facility. Please refer to "Handling and Retention of BA and BE Testing Samples", posted May 2004 for details.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CLINICAL REVIEW

Clinical Review Section

CC: ANDA 76-942
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-600/ S. Ho
HGD-600/ D. Hixon

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Endorsements: (Final with Dates)
HFD-600/S. Ho 3/28/05
HFD-600/D. Hixon 3/28/05
HFD-650/D. Conner 3/28/05

BIOEQUIVALENCY - ACCEPTABLE

submission dates:
February 5, 2004
January 4, 2005
January 18, 2008

1. Bioequivalence Study (STU); February 5, 2004 Strengths: 2%
Outcome: AC

2. Study Amendments (STA); January 4, 2005 Strengths: all
January 18, 2008 Outcome: AC

Please note: This review should close the BCE and BST assignments.

Outcome Decisions: AC - Acceptable
WC - Without charge
IC - Incomplete
UC - Unacceptable

CLINICAL REVIEW

Clinical Review Section

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #: 76-942 SPONSOR : Atrix Laboratories, Inc.

DRUG AND DOSAGE FORM : Ketoconazole Shampoo

STRENGTH(S) : 2%

TYPES OF STUDIES : Clinical Endpoint

CLINICAL STUDY SITE(S) : multiple sites in USA

ANALYTICAL SITE(S) : N/A

STUDY SUMMARY: Study is acceptable

DISSOLUTION : N/A

DSI INSPECTION STATUS

Inspection needed: YES / NO	Inspection status: N/A	Inspection results: N/A
First Generic ____ New facility ____ For cause ____ other ____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER: Sarah Ho, Pharm. D.

INITIAL : _____ DATE : 3/28/05

ASSOCIATE DIRECTOR FOR MEDICAL AFFAIRS: Dena R. Hixon, M.D.

INITIAL : DRH DATE : 3/28/05

DIRECTOR, DIVISION OF BIOEQUIVALENCE : Dale P. Conner, Pharm. D.

INITIAL : _____ DATE : 3/28/05

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-942

STATISTICAL REVIEW

Statistical Review

ANDA 76-942
Drug Product: Ketoconazole Shampoo, 2%
Sponsor: Atrix Laboratories, Inc.
Reference Listed Drug: Nizoral® Shampoo, 2%, (McNeil Consumer, NDA: 19-927, 8/31/1990).

Submission dates: December 13, 2003, February 5, 2004, January 4, and 18, 2005.

Reviewer: Mohamed Moustapha, QMRS/OB/CDER
Clinical Reviewer: Sarah Ho, Pharm.D. , OGD/CDER, 2/07/2005.

Objectives of the study

The objectives of the study were to demonstrate comparable safety and efficacy of Atrix's Ketoconazole Shampoo, 2% (Test product) to McNeil Consumer's Nizoral® Shampoo, 2%, (Reference product) in the treatment of Tinea (Pityriasis) Versicolor in order to establish bioequivalence, and to show the superiority of the active treatments over that of Atrix's Vehicle (Vehicle).

Study Design

This was a 3 arm parallel-group, double-blind, randomized, placebo-controlled, Multi-center (14 sites) study to evaluate the safety, efficacy and clinical equivalence of Atrix's Ketoconazole Shampoo (Test product) to McNeil Consumer's Nizoral® Shampoo (Reference product) in subjects diagnosed with Tinea (Pityriasis) Versicolor.

A total of 300 subjects were enrolled and randomly assigned to one of the three treatment groups in a ratio of 3:3:1 (Test: Reference: Vehicle). Subjects diagnosed with Tinea (Pityriasis) Versicolor were enrolled in the study as follow; 128 in the Test group, 130 in the Reference group, and 42 in the Vehicle group. The study was designed to have each subject performing 3 visits. Each patient was required to use the shampoo as instructed on a single occasion within three days after their baseline visit. Visit 1 was for screening prior to the first dose (Day 1), follow-up visit 2 at Day 10 (±4 days), and visit 3 at Day 31 (±4 days) were for clinical endpoints evaluations.

Outcome Variables

Primary Endpoint:

The primary endpoint used to assess efficacy and equivalence is the dichotomized (Success / Failure) Therapeutic Cure rate at visit 3 (Day 27 to 35). A patient was classified as a Therapeutic Cure if he/she had the following:

- Had a negative KOH test

- Were considered healed (no scaling, itching or erythema) based on the IGE (Investigator's Global Evaluation.)
- Had a zero score (absence) for desquamation/scaling and pruritus/itching and erythema for clinical signs and symptoms and a score no greater than two (moderate) for either hyper- or hypopigmetation.

Secondary Endpoints:

Per the OGD Medical reviewer's comments the following variables were to be analyzed as secondary endpoints:

- Therapeutic Cure rate at visit 2
- IGE at visits 2 and 3
- KOH at visits 2 and 3

The following Signs and Symptoms were to be evaluated for their presence and severity:

Investigator Global Evaluation	*Patient's evaluation Scale*
• erythema	Desquamation/Scaling
• scaling	Pruritus/Itching
• itching	Erythema
	Hyperpigmetation
	Hypopigmetation

Severity scale was defined as follows:

0 = Absent	2 = Moderate
1 = Mild	3 = severe or extensive

Analysis Populations

Two populations were evaluated for efficacy and equivalence:

- Modified-Intent-to-Treat population (MITT) –Includes all randomized subjects who met the inclusion/exclusion criteria, received at least one dose of study medication, and returned for at least one post-baseline visit evaluation. For patients who failed to return for Visit 3 or used prohibited medications between Visits 2 and 3, or who where discontinued from further participation for some other reason, their second visit (Visit 2) data was carried forward (LOCF) and used in this analysis of efficacy. This population is the primary population for efficacy analysis.

- Per Protocol population (PP) –Includes all randomized subjects who met all inclusion/exclusion criteria, used the medication within 3 days of the baseline visit, returned to the study site for visit 3 within the specified window, and did not have any protocol violations. The Per Protocol population is the primary population for bioequivalence analysis of the Test and the Reference products.

Per the OGD Clinical reviewer's comments, the LOCF should only be used for patients who failed to return for Visit 3 or who discontinued early from the study due to treatment failure.

LOCF of Visit 2 should NOT be used for patients who used prohibited medications between Visits 2 and 3 in the PP population.

Statistical Analysis Methods

Efficacy Analysis

For the superiority of each active treatment over the Vehicle, the Therapeutic Cure rates in the MITT population at visit 3 were used. In addition, per the OGD Medical reviewer's comments, additional analyses based on secondary endpoints were conducted.

Tests for superiority of each active treatment over the Vehicle were conducted using the two-sided Fisher's exact test at the 5% level of significance. The primary analysis was based on the MITT population and the Last Observation Carried Forward (LOCF) approach was used to impute for missing data in the MITT population. However a subject who did not have a post-baseline visit evaluation was excluded from analyses.

Equivalence Analysis

The standard method in OGD to Test for clinical equivalence for binary outcomes is based on the 90% confidence interval. The interval was calculated using Wald's method with Yate's continuity correction. Bioequivalence was established if this 90% confidence interval of the difference in the Therapeutic Cure rates between the Test and Reference groups at visit 3 was contained within the interval [–20%, 20%]. The analysis in the PP population was considered primary.

The null hypothesis to be tested was defined as follow:

H_0: $p_T - p_R < -.20$ or $p_T - p_R > .20$, versus, H_A: $-.20 \leq p_T - p_R \leq .20$, where:

p_T = Therapeutic Cure rate of the Test product, p_R = Therapeutic Cure rate of the Reference product.

Let n_T = Sample size of the Test product, n_R = Sample size of the Reference product.

$$se = \left(\hat{p}_T(1 - \hat{p}_T)/n_T + \hat{p}_R(1 - \hat{p}_R)/n_R \right)^{1/2}$$

The 90% confidence interval for the difference in proportions between the Test and Reference products was calculated as follows, using Yates' correction:

$$L = (\hat{p}_T - \hat{p}_R) - 1.645\ se - (1/n_T + 1/n_R)/2 \quad U = (\hat{p}_T - \hat{p}_R) + 1.645\ se + (1/n_T + 1/n_R)/2$$

We reject H_0 if $L \geq -.20$ and $U \leq .20$. Rejection of the null hypothesis H_0 supports the conclusion of equivalence of the two products.

Statistical Analysis Results

Demographic characteristics

A total of 300 patients were enrolled in the study, of whom 128 received the Test product, 130 received the Reference product, and 42 received the Vehicle product. Two hundred seventy one of these patients were qualified to be included in the Modified Intent-to-Treat (MITT) population (118 are in the Test, 119 are in the Reference, and 34 are in the Vehicle group). Of the total MITT population, 67.9% (184) are White, 7.7% (21) are Black, 21.8% (59) are Hispanic, and 2.6% (7) are of other ethnicity. One hundred fifteen patients are Male and 156 are Female, however there was no statistically significant gender difference across treatment groups.

Table 1 describes the demographic characteristics for the MITT population.

Overall, there was no statistically significant difference across treatment groups in the demographic characteristics; Gender, or Race, where p-values were, 0.36, and 0.99.

Table 1- Demographic characteristics of the MITT population

Age	Test(N = 118)	Reference (N = 119)	Vehicle(N = 34)	p-value
MAX	75	76	70	
MEAN	36	36	41	
MIN	18	18	18	0.20 [2]
N	118	119	34	
STD	15	15	13	
Race				
Caucasian	80 (67.8%)	80 (67.2%)	24 (70.6%)	
Black	8 (6.8%)	12 (10.1%)	1 (2.9%)	0.997 [1]
Hispanic	24 (20.3%)	27 (22.7%)	8 (23.5%)	
Others	6 (5.1%)	0 (0.0%)	1 (2.9%)	
Male	50 (42.4%)	51 (42.9%)	14 (41.2%)	0.36 [1]
Female	68 (57.6%)	68 (57.1%)	20 (58.8%)	

[1] p-value for treatment comparisons from Cochran-Mantel-Haenszel Test for general association.
[2] p-value for treatment comparisons from ANOVA model with treatment as covariate.

Baseline characteristics

Table 2 shows that the enrolled population consisted of 128 subjects assigned to the Test product, 130 subjects assigned to the Reference product, and 42 subjects in the Vehicle product group. However, 29 subjects were excluded from the enrolled population, leaving the MITT population with 118 subjects assigned to the Test product, 119 subjects assigned to the Reference product, and 42 subjects in the Vehicle product group. The PP population originally included 107 patients in the Test product group, 106 in the Reference product group, and 31 in the Vehicle group. However patient # 1319 (in the Test group) and patient # 1367 (in the Reference) were excluded from the PP population since they had a visit 3 outside the window (Day 27 to Day 35).

Table 2. Population distribution

Population	Test (N = 118)	Reference (N = 119)	Vehicle (N = 34)	Total (N = 271)
Subjects Enrolled	128 (100%)	130 (100%)	42 (100%)	300 (100%)
Patients Excluded from MITT	10 (8%)	11 (8%)	8 (19%)	29 (10%)
Total Patients in the MITT	118 (92%)	119 (92%)	34 (81%)	271 (90%)
Patients Excluded from PP	21 (16%)	24 (18%)	11 (26%)	56 (19%)
Total Patients in the PP	107 (84%)	106 (82%)	31 (74%)	244 (81%)

Patients # 1319 (Test), and patient # 1367 (Reference) were excluded from the PP population, leaving 106 in the Test group and 105 in the Reference group.

Signs and Symptoms as defined in a previous section (page 2), were compared across treatment groups at baseline. Erythema, Scaling, Itching, Hyperpigmentation, and Hypopigmentation were found to be comparable at baseline across the three treatment groups in the MITT population. There were no statistically significant differences between treatments in the MITT population with regard to ratings for scaling (p=0.20), Itching (p=0.60), erythema (p=0.44), Hyperpigmetation (p=0.34), or Hypopigmetation (p=0.43).

Table 3. Population Analysis distribution (reviewer's analysis)

Parameter		Test (N = 118)	Reference (N = 119)	Vehicle (N = 34)	Total (N = 271)	P-value
Scaling	None	0	0	1	1	0.20
	Mild	19	17	5	41	
	Moderate	74	77	24	175	
	Severe	25	25	4	54	
Itching	None	43	34	10	87	0.60
	Mild	37	38	14	89	
	Moderate	30	41	9	80	
	Severe	8	6	1	15	
Erythma	None	22	26	9	57	0.44
	Mild	49	40	7	96	
	Moderate	42	46	15	103	
	Severe	5	7	3	15	
Hyperpigmentation	None	68	68	12	148	0.34
	Mild	21	18	7	46	
	Moderate	25	29	13	67	
	Severe	4	4	2	10	
Hypopigmentation	None	19	23	11	53	0.43
	Mild	16	20	4	40	
	Moderate	67	58	16	141	
	Severe	16	18	3	37	

[1] p-value for treatment comparisons from the Cochran-Armitage Test for trend.

Efficacy analyses

The efficacy analyses based on the Therapeutic Cure rate at visit 3 (primary endpoint) in the MITT population showed evidence of superiority of the Test and Reference products over the Vehicle. The Tests for comparing the Test and the Reference product to the Vehicle were statistically significant (p-Value < 0.001).

In addition, comparisons based on secondary endpoints such as Investigator Global Evaluation at visit 3, and KOH at visit 3 showed the Test and the Reference products were better than Vehicle. However secondary endpoints such as Therapeutic Cure at visit 2, Investigator Global Evaluation at visit 2, and KOH at visit 2 failed to show superiority of the active over the Vehicle.

Table 4 - Efficacy Analyses based on the MITT population

Parameter	Treatment arm			p-value [1]	
	Test	Reference	Vehicle	Test vs. Vehicle	Reference vs. Vehicle
Therapeutic Cure at visit 3	***58% (69/118)***	***57% (68/119)***	***15% (5/34)***	***< 0.001***	***< 0.001***
Therapeutic Cure at visit 2	***18% (21/116)***	***21% (25/118)***	***12% (4/34)***	***0.446***	***0.322***
Investigator Global Evaluation at visit 3	***67% (79/118)***	***66% (79/119)***	***24% (8/34)***	***< 0.001***	***< 0.001***
Investigator Global Evaluation at visit 2	25% (29/118)	27% (32/119)	15% (5/34)	0.254	0.177
KOH at visit 3	***86% (101/118)***	***87% (104/119)***	***47% (16/34)***	***< 0.001***	***< 0.001***
KOH at visit 2	51% (60/118)	51% (61/119)	35% (12/34)	0.123	0.121

[1] p-values were derived from the 2-sided Fisher's exact test.

The Test and Reference products were found to be clinically equivalent for the Therapeutic Cure rate at visit 3 (primary endpoint) in the PP population. In addition, the clinical equivalence test based on secondary endpoints such as Therapeutic Cure at 2, Investigator Global Evaluation at visits 2 and 3, and KOH at visits 2 and 3 provided supportive evidence of the clinical equivalence of the Test and the Reference products. Table 5 summarizes the clinical equivalence results.

Table 5 - Bioequivalence Analyses based on the PP population

Parameter	Test	Reference	The 90% CI for the Test and Reference	Is the 90% CI within (-20%, 20%)?
Therapeutic Cure at visit 3	*62% (66/107)*	*59% (63/106)*	*(-9.7 , 14.2)*	*YES*
Therapeutic Cure at visit 2	17% (18/105)	19% (20/105)	(-11.6 , 7.8)	YES
Investigator Global Evaluation at visit 3	64% (68/107)	63% (67/106)	(-11.5 , 12.1)	YES
Investigator Global Evaluation at visit 2	24% (26/107)	25% (26/106)	(-10.9 , 10.4)	YES
KOH at visit 3	84% (90/107)	86% (91/106)	(-10.7 , 7.3)	YES
KOH at visit 2	50% (54/107)	51% (54/106)	(-12.7 , 11.7)	YES

Confidence interval calculated using Wald's method with Yates' continuity correction.

Comments on the Sponsor's Analyses

The Sponsor's primary efficacy variable was Therapeutic Cure rate at the Test-of-Cure visit (visit 3). Based on the sponsor's statistical analysis using 90% confidence intervals, the study demonstrates that the difference in the Therapeutic Cure rates between the Test and the Reference products is within [-.20, +.20] .

The sponsor's analyses, while they reach a similar conclusion with regard to bioequivalence for the primary endpoint, were based on a different PP population than that of this reviewer. Because the sponsor included two more patients in the PP population than we did, the FDA Medical reviewer requested a re-evaluation of the sponsor's data.

Efficacy (per sponsor) Using the ITT population, the cure rate for the test, reference and placebo treatment groups were 58.74%, 57.14% and 14.71%, respectively (Table 6). Both the Test and Reference products were shown to be highly significantly superior to placebo ($p<0.0001$ in both cases).

Table 6: Efficacy and Bioequivalence at Visit 3 (per sponsor)

Cure Rate (%)			p-value	
Test	Reference	Placebo	Test vs. Placebo	Reference vs. Placebo
58.47	57.14	14.71	<.0001	<.0001

Cure Rate (%)		Difference Between Treatments		
			90% Confidence Interval	
Ketoconazole Shampoo	Nizoral Shampoo	Difference	Lower Limit	Upper Limit
62.04	58.88	-3.23	-14.44	7.98

According to the sponsor's analysis, the Test and Reference products were both statistically significantly superior over the Vehicle ($p < 0.001$) for the Therapeutic cure rate. In addition, based on the Therapeutic cure rate at visit 3 (primary endpoint); the sponsor stated that the equivalence Test met the 90% CI criteria within [-.20, +.20] for both the PP and MITT populations.

Conclusion

Efficacy:

Our analysis showed that the Test and Reference products were both statistically significantly better than Vehicle in the treatment of tinea (pityriasis) versicolor for Therapeutic Cure at visit 3 (primary endpoint) in the MITT population. Additionally, analyses based on secondary endpoints showed the superiority of both the Test and Reference products over the Vehicle in the MITT population, for Investigator Global Evaluation, and KOH at visits 3.

Equivalence: The Test and Reference products were found to be clinically equivalent for all variables (primary and secondary endpoints) in the PP population.

3/31/05

Mohamed Moustapha
Mathematical Statistician, QMR

Donald J. Schuirmann 3/31/05

Donald J. Schuirmann
Expert Mathematical Statistician, QMR

Stella C. Machado 3/31/05

Stella G. Machado, Ph.D.
Director, QMR

cc: Original ANDA 76-942
HFD-600
Dena Hixon, Sarah Ho, Krista Scardina
HFD-705
Stella Machado, Donald J. Schuirmann, Mohamed Moustapha
HFD-705 QMR Chron.

This Review Includes 8 Pages, 03/23/05

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-942

ADMINISTRATIVE DOCUMENTS

RECORD OF TELEPHONE CONVERSATION

On December 16, 2004, I contacted Atrix Laboratories, Inc. (Atrix) to request the following:

1. Please provide a file (i.e., "Define.pdf") in Adobe format which explains the formats/variables of the datasets.
2. Please provide the reason(s) for each patient's exclusion from each population (in a .xpt format).
3. In the dataset, it seems that there is a column for population. Is it safe to assume that if the patient is noted to be in PPP then that patient is also included in the ITT and Safety? Also if the patient is included in the ITT then that the patient is also included in the Safety?
4. Please provide a comprehensive list of concomitant medications prior to the study and during the study in a .xpt format.
5. Please provide a list of medical history.
6. The file for the randomization code cannot be opened. Please correct the error and resend the file.

I instructed Ms. Hansen to submit Atrix's responses in electronic format. Ms. Hansen explained that she would contact ——— (the conductor of the clinical study) and respond to our request.

On December 23, 2004, Ms. Hansen contacted me and explained that the response to item #4 above would take 4 weeks if ——— coverts the information to .xpt format. I informed Ms. Hansen that for this particular study, I do not need the medical history in .xpt format. A simple table listing (on paper or .pdf format) would suffice.

DATE:
12/16/04 & 12/23/04

ANDA NUMBER
76-942

TELECON INITIATED BY AGENCY

PRODUCT NAME:
Ketoconazole Shampoo, 2%

FIRM NAME:
Atrix Laboratories, Inc.

FIRM REPRESENTATIVES:
Lynn Hansen, Regulatory Affairs Manager

TELEPHONE NUMBER:
970-212-4894

FDA REPRESENTATIVES
Sarah Ho

SIGNATURES:
S.Ho 12/30/04

Orig: ANDA 76-942
Cc: Division File

V:\FIRMSAM\ATRIX\Telecon\76942.16dec2004.doc

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-942 Applicant QLT USA, Inc. (Formerly Atrix Laboratories, Inc.
Drug Ketoconazole Shampoo Strength(s) 2%

APPROVAL ☑ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER:	DRAFT Package	FINAL Package
1. Martin Shimer Chief, Reg. Support Branch	Date 5 April 05 Initials MAS	Date Initials

Contains GDEA certification: Yes ☑ No ☐ (required if sub after 6/1/92)
Determ. of Involvement? Yes ☐ No ☐
Pediatric Exclusivity System
RLD = NDA#
Patent/Exclusivity Certification: Yes ☑ No ☐
Date Checked
If Para. IV Certification- did applicant
Nothing Submitted ☐
Notify patent holder/NDA holder Yes ☐ No ☐
Written request issued ☐
Was applicant sued w/in 45 days: Yes ☐ No ☐
Study Submitted ☐
Has case been settled: Yes ☐ No ☐ Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☑
Date of latest Labeling Review/Approval Summary 3/17/04
Any filing status changes requiring addition Labeling Review Yes ☐ No ☑
Type of Letter:
Comments: No patents/exclusivities ∴ eligible for Full Approval

2. Project Manager, Sarah Parks Team 11 Review Support Branch	Date 2/14/05 Initials SAP	Date Initials

Original Rec'd date 12/15/2003 RF 1/27/04
Date Acceptable for Filing 2/9/2004
Patent Certification (type) II
Date Patent/Exclus.expires MAY
Citizens' Petition/Legal Case Yes ☐ No ☒
(If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☒

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 4/17/04
Date of Office Bio Review 3/28/05
Date of Labeling Approv. Sum 4/6/2004
Labeling Acceptable Email Rec'd Yes ☐ No ☐
Labeling Acceptable Email filed Yes ☐ No ☐
Date of Sterility Assur. App. N/A
Methods Val. Samples Pending Yes ☐ No ☐ NA
MV Commitment Rcd. from Firm Yes ☐ No ☐

Acceptable Bio reviews tabbed Yes ☒ No ☐
Suitability Petition/Pediatric Waiver
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Modified-release dosage form: Yes ☐ No ☒
Interim Dissol. Specs in AP Ltr: Yes ☐
Previously reviewed and tentatively approved ☐ Date
Previously reviewed and CGMP def. /NA Minor issued ☐ Date
Comments:

3. David Read **(PP IVs Only)** OGD Regulatory Counsel,	Pre-MMA Language included ☐ Post-MMA Language Included ☐	Date Initials

Comments:

4. Div. Dir./Deputy Dir. Chemistry Div. I II OR III		Date 4/6/05 Initials

Comments: more satisfactory

REVIEWER: **FINAL ACTION**

5. Frank Holcombe **First Generics Only** Date_____
Assoc. Dir. For Chemistry Initials_____
Comments: (First generic drug review)

6. Vacant Date_____
Deputy Dir., DLPS Initials_____

7. Peter Rickman Date 4/11/05
Director, DLPS Initials_____
Para.IV Patent Cert: Yes ☐ No ☐; Pending Legal Action: Yes ☐ No ☐; Petition: Yes☐ No☐
Comments:

No patents or exclusivity issues Full approval
Labeling acceptable 4/16/04
Bio acceptable 3/28/2005 (Clinical endpoint) STATS review acceptable 3/31/2005
EER acceptable 11/17/2004

OR

8. Robert L. West Date _____
Deputy Director, OGD Initials _____
Para.IV Patent Cert: Yes☐ No☐; Pending Legal Action: Yes☐ No☐; Petition: Yes☐ No☐
Comments:

9. Gary Buehler Date 4/11/05
Director, OGD Initials GB
Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐

10. Project Manager, Team 11 Date 4/11/05
Review Support Branch Initials SLP
N/A Date PETS checked for first generic drug (just prior to notification to firm)
Applicant notification:
2:20 Time notified of approval by phone 2:20 Time approval letter faxed
FDA Notification:
4/11/2005 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
4/11/2005 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

Approval Letter Faxed to Orange Book Staff @ 301-827-7337: Date/Time: 4/11/05 2:30p

File V:/division/dlps/approvrou9.doc

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-942

CORRESPONDENCE

ANDA 76-942

Atrix Laboratories, Inc.
Attention: Cheri Jones
2579 Midpoint Drive
Fort Collins, CO 80525-4417

JAN 27 2004

Dear Madam:

Please refer to your abbreviated new drug application (ANDA) dated December 13, 2003, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Ketoconazole Shampoo, 2%.

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to receive this ANDA under 21 CFR 314.101(d)(3) for the following reasons:

> The concentration of the inactive ingredient sodium laureth sulfate in your proposed formulation for Ketoconazole Shampoo, 2% exceeds the maximum concentration of this inactive ingredient previously approved by the Agency in a topical drug product. Therefore, the proposed drug product cannot be received as an ANDA. Please provide examples of approved drug products administered by the same route of administration which contain this inactive ingredient in the same concentration range or provide information demonstrating that this inactive ingredient in this concentration does not affect the safety of the proposed drug product.

Thus, it will not be received as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

Upon receipt of this communication, you may either amend your application to correct the deficiencies or withdraw your application under 21 CFR 314.99. If you have any questions please call:

Paras Patel
Project Manager
(301) 827-5862

Sincerely yours,

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 76-942
cc: DUP/Jackets
HFD-600/Division File
Field Copy
HFD-610/G. Davis
HFD-92

Endorsement: HFD-615/MShimer, Chief, RSB date 26 Jan 2004
HFD-615/PPatel, CSO date 1/23/04
Word File V:\Firmsam\Atrix\ltrs&rev\76942.RTR
F/T File P.M.P 1/23/04
ANDA Refuse to Receive!

2579 MIDPOINT DRIVE
FORT COLLINS, CO 80525-4417
U.S.A.

ATRIX
LABORATORIES, INC.

Regulatory Affairs
PHONE: (970) 212-4901
FAX: (970) 482-9734
http://www.atrixlabs.com

February 5, 2004

Gary Buehler
Acting Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NIAC

Re: ANDA 76-942: Ketoconazole Shampoo, 2%
Resubmission - Response to Refuse to Receive Letter

Dear Mr. Buehler,

In response to the letter dated January 27, 2004, Atrix Laboratories, Inc. (ATRIX) hereby submits an updated chemistry section clarifying the amount of sodium laurel sulfate used in the final Ketoconazole Shampoo, 2% product.

Response to Refuse to Receive is acceptable. P.M.P 2/17/03

The concentration range of the inactive ingredient sodium laureth sulfate used in the final Ketoconazole Shampoo, 2% product is between [redacted]. Please refer to page 10, paragraph two of the electronic chemistry section for a complete explanation as to the concentration of sodium laureth sulfate used in the final product. Furthermore, the following documents have been updated to indicate that the raw material sodium laureth sulfate is [redacted]:

- Bulk Production Record 90186A.003, Ketoconazole Shampoo, 2%
- Raw Material Specification 01162.007, Sodium Laureth Sulfate [redacted]
- Certificate of Analysis 01162.007, Sodium Laureth Sulfate [redacted]

This application includes an updated electronic chemistry section, table of contents, cover letter and FDA 356h form, as well as a hard copy of the 356h form and cover letter. Other required documentation was previously submitted with the original ANDA application dated December 13, 2003. ATRIX certifies that the CD-ROM has been scanned for viruses using Symantec Antivirus Corporate Edition version 8.00.0.9347 with current virus definitions and is virus free. The Field Office will be notified of our resubmission of this ANDA.

Should you have any additional questions regarding this ANDA, please contact me by telephone (970-212-4901) or by email: cjones@atrixlabs.com.

Sincerely,
Atrix Laboratories, Inc.

Cheri Jones

Cheri Jones, M.S., RAC
Vice President Regulatory Affairs

RECEIVED
FEB 09 2004
HFD-530/ORDER

ANDA 76-942

Atrix Laboratories, Inc.
Attention: Cheri Jones
2579 Midpoint Drive
Fort Collins, CO 80525-4417

FEB 18 2004

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to our "Refuse to Receive" letter dated January 27, 2004 and to your amendment dated February 5, 2004.

NAME OF DRUG: Ketoconazole Shampoo, 2%

DATE OF APPLICATION: December 13, 2003

DATE (RECEIVED) ACCEPTABLE FOR FILING: February 9, 2004

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Wanda Phamphile
Project Manager
(301) 827-5848

Sincerely yours,

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 76-942
cc: DUP/Jackets
HFD-600/Division File
Field Copy
HFD-610/G. Davis
HFD-92
Endorsement:
HFD-615/MShimer,Chief, RSB _____ date 18 Feb 2004
HFD-615/PPatel,CSO _____ date 2/17/04
Word File V:\Firmsam\Atrix\ltrs&rev\76942.ACK
F/T P.M.P 2/17/04
ANDA Acknowledgment Letter!

APPEARS THIS WAY
ON ORIGINAL

2579 MIDPOINT DRIVE
FORT COLLINS, CO 80525-4417
U.S.A.

ATRIX
LABORATORIES, INC.

Regulatory Affairs
PHONE: (970) 212-4901
FAX: (970) 482-9734
http://www.atrixlabs.com

March 18, 2004

Gary Buehler, R.Ph.
Acting Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: ANDA 76-942: Ketoconazole Shampoo, 2%
Labeling Amendment – Final Printed Labeling

ORIG AMENDMENT
N/AF

Dear Mr. Buehler,

In response to the minor labeling deficiencies received on March 17, 2004, Atrix Laboratories, Inc. (ATRIX) hereby submits final printed labeling. The labeling has been updated as requested by the Agency.

This application includes an updated electronic labeling section, table of contents, cover letter and FDA 356h form, as well as a hard copy of the 356h form and cover letter. Other required documentation was previously submitted with the original ANDA application dated December 13, 2003, or in the Response to the Refuse to Receive Letter dated February 5, 2004. ATRIX certifies that the CD-ROM has been scanned for viruses using Symantec Antivirus Corporate Edition version 8.00.0.9347 with current virus definitions and is virus free.

Should you have any additional questions regarding this ANDA, please contact me by telephone (970-212-4901) or by email: cjones@atrixlabs.com.

Sincerely,
Atrix Laboratories, Inc.

Cheri Jones

Cheri Jones, M.S., RAC
Vice President Regulatory Affairs

RECEIVED
MAR 19 2004
OGD/CDER

2579 MIDPOINT DRIVE
FORT COLLINS, CO 80525-4417
U.S.A.

ATRIX
LABORATORIES, INC.

Regulatory Affairs
PHONE: (970) 212-4901
FAX: (970) 482-9734
http://www.atrixlabs.com

April 5, 2004

ORIG AMENDMENT

AF

Gary Buehler, R.Ph.
Acting Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: ANDA 76-942: Ketoconazole Shampoo, 2%
Amendment to 03/18/04 Labeling Amendment – Final Printed Labeling

Dear Mr. Buehler,

In response to the minor labeling deficiencies received on March 17, 2004, and a phone call from Ms. Ruby Wu on March 31, 2004, Atrix Laboratories, Inc. (ATRIX) hereby submits final printed labeling. The labeling has been updated with revision numbers and the date of revision as requested by the Agency.

This application includes an updated electronic labeling section, table of contents, cover letter and FDA 356h form, as well as a hard copy of the 356h form and cover letter. Other required documentation was previously submitted with the original ANDA application dated December 13, 2003, or in the Response to the Refuse to Receive Letter dated February 5, 2004. ATRIX certifies that the CD-ROM has been scanned for viruses using Symantec Antivirus Corporate Edition version 8.00.0.9347 with current virus definitions and is virus free.

Should you have any additional questions regarding this ANDA, please contact me by telephone (970-212-4901) or by email: cjones@atrixlabs.com.

Sincerely,
Atrix Laboratories, Inc.

Cheri Jones

Cheri Jones, M.S., RAC
Vice President Regulatory Affairs

RECEIVED
APR 0 6 2004
OGD/ODER

2579 MIDPOINT DRIVE
FORT COLLINS, CO 80525-4417
U.S.A.

ATRIX
LABORATORIES, INC.

Regulatory Affairs
PHONE: (970) 212-4901
FAX: (970) 482-9734
http://www.atrixlabs.com

August 13, 2004

Gary Buehler
Acting Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N1AM

Re: Minor Deficiency

ANDA 76-942

Ketoconazole Shampoo, 2%

Dear Mr. Buehler:

Atrix Laboratories Inc. is submitting a Minor Amendment to Abbreviated New Drug Application (ANDA) 76-942 seeking approval for Ketoconazole Shampoo 2%.

This amendment to a pending application is being submitted in response to the Agency Minor Deficiency Letter dated July 29, 2004. In accordance with 21 CFR 314.120 Atrix is amending the deficiencies listed for ANDA 76-942.

A. Deficiencies:

[redacted]

Redacted 4 page(s)

of trade secret and/or

confidential commercial

information from

8/13/2004 ATRIX LETTER

4) Your bioequivalence information is pending review. Deficiencies, if any, will be communicated to you separately.

Atrix Response: Acknowledged

This submission contains one volume of required signed original documents to accompany the electronic version in accordance with FDA-OGD guidelines. This Minor Deficiency Response is an electronic submission per OGD electronic format for ANDAs, provided on one CD-ROM, approximately 20 KB. ATRIX certifies that the CD-ROM has been scanned for viruses using Symantec Antivirus Corporate Edition version 8.00.0.9347 with current virus definitions and is virus free.

Should you have any additional questions regarding this ANDA, please contact me by telephone (970-212-4901) or by email: cjones@Atrixlabs.com.

Sincerely,

Cheri Jones, M.S., R.A.C.
Vice President, Regulatory Affairs
ATRIX Laboratories, Inc.

August 18, 2004

ORIG AMENDMENT

N/AM

Gary Buehler

Acting Director, Office of Generic Drugs

Office of Generic Drugs, CDER, FDA

Document Control Room, Metro Park North II

7500 Standish Place, Room 150

Rockville, MD 20855-2773

Re: Amendment to Minor Deficiency, ANDA 76-942, Ketoconazole Shampoo, 2%

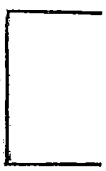
Dear Mr. Buehler:

Atrix Laboratories Inc. is submitting an Amendment to the Minor Amendment to Abbreviated New Drug submitted to the ANDA on 8/13/04. This amendment follows a discussion with the CMC reviewer who has reviewed the 8/13/04 amendment while at the manufacturing facility for a preapproval site inspection.

A. Deficiencies:

(1) Item #1b of Deficiency letter and 8/13/04 response)

Regarding the Drug Substance, we have the following comments:



Redacted 2 page(s)

of trade secret and/or

confidential commercial

information from

8/18/2004 ATRIX LETTER

September 02, 2004

ORIG AMENDMENT

N/A M

Gary Buehler

Acting Director, Office of Generic Drugs

Office of Generic Drugs, CDER, FDA

Document Control Room, Metro Park North II

7500 Standish Place, Room 150

Rockville, MD 20855-2773

Re: Minor Amendment to ANDA 76-942, Ketoconazole Shampoo, 2% - Reviewer Request During Manufacture Site Inspection

Dear Mr. Buehler,

Atrix Laboratories Inc. is submitting a Minor Amendment to ANDA 76-942, Ketoconazole Shampoo, 2%. This amendment follows a discussion with the CMC reviewer during the manufacturing facility pre-approval site inspection.

Per the reviewer's request we are providing a Certificate of Analysis reporting the related substance levels of the innovator product Nizoral® 2% Shampoo at or near expiry (June, 2004). Also included are the related substance chromatograms for the Nizoral® product. A table comparing the related substance values for the innovator and Atrix products is provided below.

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SEP 0 3 2004

OGD/CDER

APPEARS THIS WAY
ON ORIGINAL

Table 1: Atrix and Nizoral® Related Substance Levels

Characteristic: Limit of Related Substance (%)	Nizoral®	Atrix Ketoconazole Shampoo, 2% (12 month data) CU	CD	Atrix Proposed Shelf-life Acceptance Criteria

This completes all issues described in the Minor Deficiency and those discussed with the reviewer. We are hopeful for an approval of this ANDA as we believe all requirements for this submission have been met.

ATRIX certifies that the CD-ROM has been scanned for viruses using Symantec Antivirus Corporate Edition version 8.00.0.9347 with current virus definitions and is virus free. Should you have any further questions, please contact Michael Abernathy at (970) 212-4976 or me at (970) 212-4901.

Best regards,

For Cheri Jones

Cheri Jones, M.S., RAC

Vice President Regulatory Affairs

QLT USA, Inc.

2579 Midpoint Drive
Fort Collins, CO, USA
80525

t. 970.482.5868

www.qltinc.com

January 3, 2005

N/xS

Gary Buehler, Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

Re: ANDA 76-942
Unsolicited Supplement – Company Name Change
from Atrix Laboratories, Inc. to QLT USA, Inc.

Dear Mr. Buehler:

This notification to the application referenced above informs the Agency that all rights to the above referenced application have been transferred from Atrix Laboratories, Inc. to the new owner, **QLT USA, Inc.**, 2579 Midpoint Drive, Fort Collins, CO 80525.

Atrix Laboratories, Inc. was acquired by **QLT Inc.**, Vancouver, Canada on November 19, 2004. The change in ownership was effective on that date. Atrix Laboratories became **QLT USA, Inc.** on that date.

QLT USA, Inc. commits to all agreements, promises and conditions made by the former owner, Atrix Laboratories, Inc. in the application.

QLT USA, Inc. has a complete copy of the approved application, including supplements and records that are required to be kept under Sec. 314.81.

QLT USA, Inc. shall advise FDA about any change in the conditions in the approved application under Sec. 314.70. The drug product's label/labeling change to reflect this ownership change will be reported in the product's next annual report when revised.

Attached please find an updated 356h form signed by **QLT USA, Inc.**

I will remain the primary contact under the new organization representing regulatory affairs. You can contact me at: 970-212-4901 or email cjones@qltinc.com.

Sincerely,

QLT USA, Inc.

Cheri Jones, M.S., RAC
Vice President Regulatory Affairs

QLT USA, Inc.
2579 Midpoint Drive
Fort Collins, CO, USA
80525
t. 970.482.5868
www.qltinc.com

January 04, 2005

ORIG AMENDMENT
N/AB

Gary Buehler
Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Minor Amendment to ANDA 76-942, Ketoconazole Shampoo, 2% - Clinical Reviewer Request for Additional Data Sort

Dear Mr. Buehler,

Minor Amendment to ANDA 76-942, Ketoconazole Shampoo, 2% is submitted following discussions on December 16 & 22, 2004 with Sarah Ho, Clinical reviewer:

1) Provide a file that lists all the variables and formats and name it as define.pdf.
2) Patient Population – Identify why each patient was excluded from the PP population.
3) Listing of concomitant medications for each patient, prior to beginning the study and during the study. Define when, how long and route of administration for each patient. Needs to be provided in SAS data set form and as a transfer file.
4) List of Medical History and the disease state for each patient. Provided in SAS data set form and as a transfer file.

Per the reviewer's request we are providing the updated SAS, export and pdf files on the enclosed CD-ROM.

We certify that the CD-ROM has been scanned for viruses using Symantec Antivirus Corporate Edition version 9.00.0.338 with current virus definitions and is virus free. Should you have any further questions, please contact Lynn Hansen at (970) 212-4894 or me at (970) 212-4901.

Best regards,

Cheri Jones

Cheri Jones, M.S., RAC
Vice President Regulatory Affairs

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JAN 0 5 2005
OGD / CDER

QLT USA, Inc.

2579 Midpoint Drive
Fort Collins, CO, USA
80525

t. 970.482.5868

www.qltinc.com

ORIG AMENDMENT
N/AB

January 18, 2005

Gary Buehler
Director, Office of Generic Drugs
Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: Minor Amendment to ANDA 76-942, Ketoconazole Shampoo, 2% - Clinical Reviewer Request for Additional Data - Medical History

Dear Mr. Buehler,

Minor Amendment to ANDA 76-942, Ketoconazole Shampoo, 2% is being submitted following discussions with Sarah Ho, Clinical reviewer on December 16 & 22, 2004 and January 12, 2005. The Medical History information is now provided as a pdf file. As agreed upon with the reviewer we are providing pdf files of the CRF Medical History pages on the enclosed CD-ROM.

We certify that the CD-ROM has been scanned for viruses using Symantec Antivirus Corporate Edition version 9.00.0.338 with current virus definitions dated 01/12/2005 Rev. 16 and is virus free. Should you have any further questions, please contact Lynn Hansen at (970) 212-4894 or me at (970) 212-4901.

Best regards,

Cheri Jones

Cheri Jones, M.S., RAC
Vice President Regulatory Affairs

RECEIVED
JAN 19 2005
OGD / CDER