CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 65-112

Name: Erythromycin and Benzoyl Peroxide Topical Gel USP, 3% / 5%

Sponsor: Atrix Laboratories, Inc.

Approval Date: March 29, 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-112

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-112

APPROVAL LETTER

ANDA 65-112

MAR 29 2004

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

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated November 30, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Erythromycin and Benzoyl Peroxide Topical Gel USP, 3%/5%. We note that this product is subject to the exception provisions of Section 125 (d) (2) of Title I of the Food and Drug Administration Modernization Act of 1997.

Reference is also made to your amendments dated February 23, March 1, March 15, March 16, and March 19, 2004, and to your correspondence dated November 5, 2003.

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 Erythromycin and Benzoyl Peroxide Topical Gel USP, 3%/5% to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Benzamycin® Topical Gel of Dermik Laboratories).

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.

Post-marketing 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.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FDA 2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

Gary Buehler 3/29/04
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 65-112
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205
HFD-610/Orange Book Staff

Endorsements:
HFD-629/G.Kang/ GK 3/24/04 GK 3/11/04
HFD-623/J.Fan/ 3/11/04 3/17/04 3/24/04
HFD-617/T.Vu/ 3/18/04
HFD-617/M.Dillahunt/ 3/15/04
HFD-613/L.Golson/ 3/15/04

Robert Lyn West
3/29/2004

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F/T by

APPROVAL

PS 3/24/04

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-112

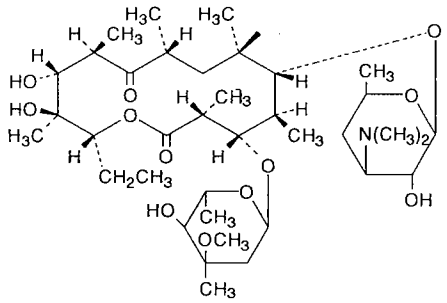
APPROVED LABELING

For Dermatologist Use Only – Not for Ophthalmic Use
Reconstitute Before Dispensing

DESCRIPTION: Erythromycin and Benzoyl Peroxide Topical Gel, USP contains erythromycin [(3*R**, 4*S**, 5*S**, 6*R**, 7*R**, 9*R**, 11*R**, 12*R**, 13*S**, 14*R**)-4-[(2,6-Dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)-oxy]-14-ethyl-7,12,13-trihydroxy-3,5,7,9,11,13-hexa-methyl-6-[[3,4,6-trideoxy-3-(dimethylamino)-ß-D-*xylo*-hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione]

Erythromycin is a macrolide antibiotic produced from a strain of *Saccharopolyspora erythraea* (formerly *Streptomyces erythreus*). It is a base and readily forms salts with acids.

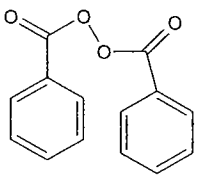
Chemically, erythromycin is ($C_{37}H_{67}NO_{13}$). It has the structural formula:



Erythromycin has the molecular weight of 733.94. It is a white crystalline powder and has a solubility of approximately 1 mg/mL in water and is soluble in alcohol at 250C.

Erythromycin and Benzoyl Peroxide Topical Gel also contains benzoyl peroxide for topical use. Benzoyl peroxide is an antibacterial and keratolytic agent.

Chemically, benzoyl peroxide is ($C_{14}H_{10}O_4$). It has the following structural formula:



Benzoyl peroxide has the molecular weight of 242.23. It is a white granular powder and is sparingly soluble in water and alcohol and soluble in acetone, chloroform and ether.

Each gram of Erythromycin and Benzoyl Peroxide Topical Gel contains, as dispensed, 30 mg (3%) of erythromycin and 50 mg (5%) of benzoyl peroxide in a base of purified water, ethyl alcohol, carbomer, sodium hydroxide, docusate sodium and fragrance.

CLINICAL PHARMACOLOGY: The exact mechanism by which erythromycin reduces lesions of acne vulgaris is not fully known; however, the effect appears to be due in part to the antibacterial activity of the drug.

Benzoyl peroxide has a keratolytic and desquamative effect which may also contribute to its efficacy. Benzoyl peroxide has been shown to be absorbed by the skin where it is converted to benzoic acid.

MICROBIOLOGY: Erythromycin acts by inhibition of protein synthesis in susceptible organisms by reversibly binding to 50 *S* ribosomal subunits, thereby inhibiting translocation of aminoacyl transfer-RNA and inhibiting polypeptide synthesis. Antagonism has been demonstrated *in vitro* between erythromycin, lincomycin, chloramphenicol and clindamycin.

Benzoyl peroxide is an antibacterial agent which has been shown to be effective against *Propionibacterium acnes*, an anaerobe found in sebaceous follicles and comedones. The antibacterial action of benzoyl peroxide is believed to be due to the release of active oxygen.

APPROVED

INDICATIONS AND USAGE: Erythromycin and Benzoyl Peroxide Topical Gel is indicated for the topical treatment of acne vulgaris.

CONTRAINDICATIONS: Erythromycin and Benzoyl Peroxide Topical Gel is contraindicated in those individuals who have shown hypersensitivity to any of its components.

WARNINGS: Pseudomembranous colitis has been reported with nearly all antibacterial agents, including erythromycin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

PRECAUTIONS:

General: For topical use only; not for ophthalmic use. Concomitant topical acne therapy should be used with caution because a possible cumulative irritancy effect may occur, especially with the use of peeling, desquamating or abrasive agents. If severe irritation develops, discontinue use and institute appropriate therapy.

The use of antibiotic agents may be associated with the overgrowth of nonsusceptible organisms including fungi. If this occurs, discontinue use and take appropriate measures.

Avoid contact with eyes and all mucous membranes.

Information for Patients: Patients using Erythromycin and Benzoyl Peroxide Topical Gel should receive the following information and instructions:

1. This medication is to be used as directed by the physician. It is for external use only. Avoid contact with the eyes, nose, mouth, and all mucous membranes.
2. This medication should not be used for any disorder other than that for which it was prescribed.
3. Patients should not use any other topical acne preparation unless otherwise directed by physician.
4. Patients should report to their physician any signs of local adverse reactions.
5. Erythromycin and Benzoyl Peroxide Topical Gel may bleach hair or colored fabric.
6. Keep product refrigerated and discard after 3 months.

CARCINOGENESIS, MUTAGENESIS AND IMPAIRMENT OF FERTILITY: Data from a study using mice known to be highly susceptible to cancer suggests that benzoyl peroxide acts as a tumor promoter. The clinical significance of this is unknown.

No animal studies have been performed to evaluate the carcinogenic and mutagenic potential or effects on fertility of topical erythromycin. However, long-term (2-year) oral studies in rats with erythromycin ethylsuccinate and erythromycin base did not provide evidence of tumorigenicity. There was no apparent effect on male or female fertility in rats fed erythromycin (base) at levels up to 0.25% of diet.

Pregnancy: Teratogenic Effects: Pregnancy CATEGORY C: Animal reproduction studies have not been conducted with Erythromycin and Benzoyl Peroxide Topical Gel or benzoyl peroxide.

There was no evidence of teratogenicity or any other adverse effect on reproduction in female rats fed erythromycin base (up to 0.25% diet) prior to and during mating, during gestation and through weaning of two successive litters.

There are no well-controlled trials in pregnant women with Erythromycin and Benzoyl Peroxide Topical Gel. It also is not known whether Erythromycin and Benzoyl Peroxide Topical Gel can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Erythromycin and Benzoyl Peroxide Topical Gel should be given to a pregnant woman only if clearly needed.

Nursing Women: It is not known whether Erythromycin and Benzoyl Peroxide Topical Gel is excreted in human milk after topical application. However, erythromycin is excreted in human milk following oral and parenteral erythromycin administration. Therefore, caution should be exercised when erythromycin is administered to a nursing woman.

Pediatric Use: Safety and effectiveness of this product in pediatric patients below the age of 12 have not been established.

ADVERSE REACTIONS: In controlled clinical trials, the total incidence of adverse reactions associated with the use of Erythromycin and Benzoyl Peroxide Topical Gel was approximately 3%. These were dryness and urticarial reaction.

The following additional local adverse reactions have been reported occasionally: irritation of the skin including peeling, itching, burning sensation, erythema, inflammation of the face, eyes and nose, and irritation of the eyes. Skin discoloration, oiliness and tenderness of the skin have also been reported.

(See Reverse)

MAR 29 2004

ERYTHROMYCIN AND BENZOYL PEROXIDE TOPICAL GEL, USP

Topical gel: erythromycin (3%), benzoyl peroxide (5%)

R_x only

PLEASE READ COMPLETE COMPOUNDING DIRECTIONS

NOTE: TAP UNTIL ALL POWDER FLOWS FREELY. ADD ETHYL ALCOHOL (70%) TO VIAL (TO THE MARK) AND **IMMEDIATELY** SHAKE/DISSOLVE **COMPLETELY.**

ENLARGED TO 115%
BY FOIA STAFF

DOSAGE AND ADMINISTRATION: Erythromycin and Benzoyl Peroxide Topical Gel should be applied twice daily, morning and evening, or as directed by a physician, to affected areas after the skin is thoroughly washed, rinsed with warm water and gently patted dry.

How Supplied and Compounding Directions:

Size (Net Weight)	NDC 0781-	Benzoyl Peroxide Gel	Active Erythromycin Powder (In Plastic Vial)	Ethyl Alcohol (70%) To Be Added
23.3 grams (as dispensed)	7054-49	20 grams	0.8 grams	3 mL
46.6 grams (as dispensed)	7054-59	40 grams	1.6 grams	6 mL

TO THE PHARMACIST: IMPORTANT – Prior to dispensing, tap vial until powder flows freely. Add indicated amount of ethyl alcohol (70%) to vial (to the mark) and immediately shake to completely dissolve erythromycin. Add this solution to gel and stir with supplied spatula until homogeneous in appearance (1 to 1 1/2 minutes). Erythromycin and Benzoyl Peroxide Topical Gel should then be stored under refrigeration. Do not freeze. Place a 3-month expiration date on the label.

NOTE: Prior to reconstitution, store at room temperature between 15° and 30°C (59°-86°F).
After reconstitution, store under refrigeration between 2° and 8°C (36° -46°F).

Do not freeze. Keep tightly closed. Keep out of the reach of children.

8071-1
Rev. 08-2002M

Manufactured By
Atrix Laboratories, Inc.
Fort Collins, CO 80526

Distributed By
Geneva Pharmaceuticals, Inc.
Broomfield, CO 80020

ENLARGED TO 115%
BY FDLA STAFF

Erythromycin

Net Wt. 1.6 grams active erythromycin. **℞ only**

TO THE PHARMACIST: IMPORTANT
Prior to dispensing, tap vial until all powder flows freely. Add 6 mL of ethyl alcohol (70%) to vial (to the mark) and immediately shake to completely dissolve erythromycin. Add solution to gel and stir until hemogeneous in appearance (1 to 1½ minutes). Final formulation should be stored in a refrigerator. Do not freeze. Label with an expiration date of 3 months.

Not for separate dispensing.

For external use only. KEEP AWAY FROM EYES. **KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.**

Rev. 08-2002M

Manufactured By
Atrix Laboratories, Inc., Fort Collins, CO 80526

APPROVED

65112

MAR 29 2004

Erythromycin

Net Wt. 0.8 grams active erythromycin. **℞ only**

TO THE PHARMACIST: IMPORTANT
Prior to dispensing, tap vial until all powder flows freely. Add 3 mL of ethyl alcohol (70%) to vial (to the mark) and immediately shake to completely dissolve erythromycin. Add solution to gel and stir until hemogeneous in appearance (1 to 1½ minutes). Final formulation should be stored in a refrigerator. Do not freeze. Label with an expiration date of 3 months.

Not for separate dispensing.

For external use only. KEEP AWAY FROM EYES. **KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.**

Rev. 08-2002M

Manufactured By
Atrix Laboratories, Inc., Fort Collins, CO 80526

APPROVED

65112

MAR 29 2004

Directions: Apply twice daily, morning and evening, or as directed by physician, to affected areas after skin is thoroughly washed, rinsed with warm water and gently patted dry. For complete product information, see package insert. Use within 3 months after mixing. Store mixed formulation in refrigerator. Do not freeze. Precautions: For external use only. Keep away from eyes. **KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.** Keep tightly closed.

NDC 0781-7054-59

Erythromycin and Benzoyl Peroxide Topical Gel, USP

Topical gel: erythromycin (3%), benzoyl peroxide (5%)

Description – After reconstitution, each gram contains 30 mg (3%) active erythromycin and 50 mg (5%) benzoyl peroxide in a gel vehicle of purified water, ethyl alcohol 70%, carbomer, sodium hydroxide, docusate sodium and fragrance.

Net Wt. 46.6 grams (as dispensed) **℞ only**

Dist. By Geneva Pharmaceuticals Broomfield, CO 80020

Mfg. By Atrix Laboratories, Inc.
Fort Collins, CO 80526
Rev. 08-2002M

APPROVED

65-112

MAR 29 200

Directions: Apply twice daily, morning and evening, or as directed by physician, to affected areas after skin is thoroughly washed, rinsed with warm water and gently patted dry. For complete product information, see package insert. Use within 3 months after mixing. Store mixed formulation in refrigerator. Do not freeze. Precautions: For external use only. Keep away from eyes. **KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.** Keep tightly closed.

NDC 0781-7054-49

Erythromycin and Benzoyl Peroxide Topical Gel, USP

Topical gel: erythromycin (3%), benzoyl peroxide (5%)

Description – After reconstitution, each gram contains 30 mg (3%) active erythromycin and 50 mg (5%) benzoyl peroxide in a gel vehicle of purified water, ethyl alcohol 70%, carbomer, sodium hydroxide, docusate sodium and fragrance.

Net Wt. 23.3 grams (as dispensed) **℞ only**

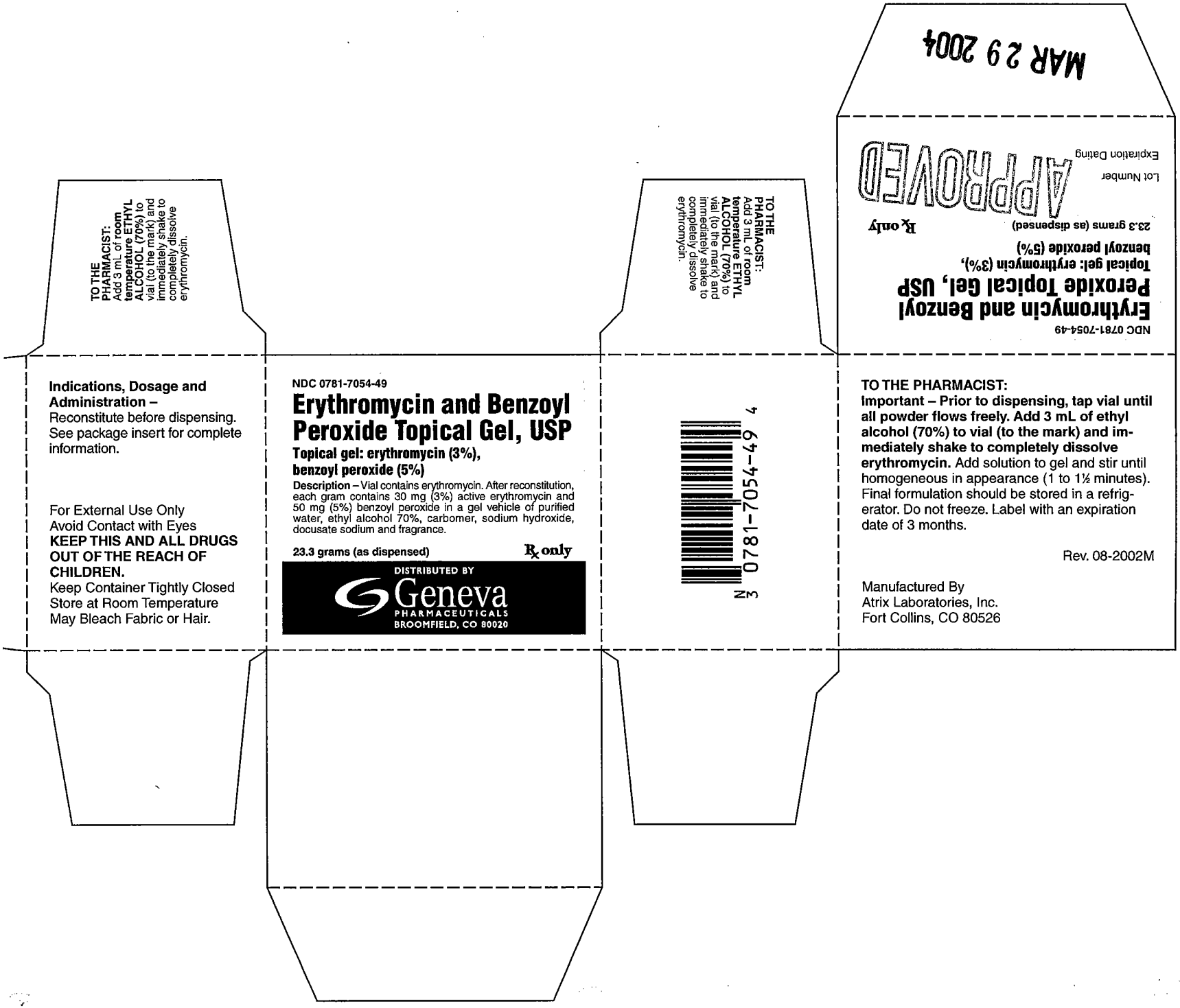
Dist. By Geneva Pharmaceuticals Broomfield, CO 80020

Mfg. By Atrix Laboratories, Inc.
Fort Collins, CO 80526
Rev. 08-2002M

APPROVED

65112

MAR 29 2004



TO THE PHARMACIST:
Add 3 mL of **room temperature ETHYL ALCOHOL (70%)** to vial (to the mark) and immediately shake to completely dissolve erythromycin.

Indications, Dosage and Administration –
Reconstitute before dispensing. See package insert for complete information.

For External Use Only
Avoid Contact with Eyes
KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.
Keep Container Tightly Closed
Store at Room Temperature
May Bleach Fabric or Hair.

NDC 0781-7054-49

Erythromycin and Benzoyl Peroxide Topical Gel, USP

Topical gel: erythromycin (3%), benzoyl peroxide (5%)

Description – Vial contains erythromycin. After reconstitution, each gram contains 30 mg (3%) active erythromycin and 50 mg (5%) benzoyl peroxide in a gel vehicle of purified water, ethyl alcohol 70%, carbomer, sodium hydroxide, docusate sodium and fragrance.

23.3 grams (as dispensed) **℞ only**

DISTRIBUTED BY
Geneva
PHARMACEUTICALS
BROOMFIELD, CO 80020

TO THE PHARMACIST:
Add 3 mL of **room temperature ETHYL ALCOHOL (70%)** to vial (to the mark) and immediately shake to completely dissolve erythromycin.

4 64-7054-49 0781 3

MAR 29 2004

APPROVED

Lot Number
Expiration Dating

23.3 grams (as dispensed) **℞ only**

NDC 0781-7054-49

Erythromycin and Benzoyl Peroxide Topical Gel, USP

Topical gel: erythromycin (3%), benzoyl peroxide (5%)

TO THE PHARMACIST:
Important – Prior to dispensing, tap vial until all powder flows freely. Add 3 mL of ethyl alcohol (70%) to vial (to the mark) and immediately shake to completely dissolve erythromycin. Add solution to gel and stir until homogeneous in appearance (1 to 1½ minutes). Final formulation should be stored in a refrigerator. Do not freeze. Label with an expiration date of 3 months.

Rev. 08-2002M

Manufactured By
Atrix Laboratories, Inc.
Fort Collins, CO 80526

TO THE PHARMACIST:
Add 6 mL of **room temperature ETHYL ALCOHOL (70%)** to vial (to the mark) and immediately shake to completely dissolve erythromycin.

Indications, Dosage and Administration –
Reconstitute before dispensing. See package insert for complete information.

For External Use Only
Avoid Contact with Eyes
KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.
Keep Container Tightly Closed
Store at Room Temperature
May Bleach Fabric or Hair.

NDC 0781-7054-59

Erythromycin and Benzoyl Peroxide Topical Gel, USP

Topical gel: erythromycin (3%), benzoyl peroxide (5%)

Description – Vial contains erythromycin. After reconstitution, each gram contains 30 mg (3%) active erythromycin and 50 mg (5%) benzoyl peroxide in a gel vehicle of purified water, ethyl alcohol 70%, carbomer, sodium hydroxide, docusate sodium and fragrance.

46.6 grams (as dispensed) **℞ only**

DISTRIBUTED BY
Geneva
PHARMACEUTICALS
BROOMFIELD, CO 80020

APPROVED
MAR 29 2004

TO THE PHARMACIST:
Add 6 mL of **room temperature ETHYL ALCOHOL (70%)** to vial (to the mark) and immediately shake to completely dissolve erythromycin.

3 0781-7054-59

NDC 0781-7054-59

Erythromycin and Benzoyl Peroxide Topical Gel, USP

Topical gel: erythromycin (3%), benzoyl peroxide (5%)

46.6 grams (as dispensed) **℞ only**

Lot Number
Expiration Dating

TO THE PHARMACIST:
Important – Prior to dispensing, tap vial until all powder flows freely. Add 6 mL of ethyl alcohol (70%) to vial (to the mark) and immediately shake to completely dissolve erythromycin. Add solution to gel and stir until homogeneous in appearance (1 to 1½ minutes). Final formulation should be stored in a refrigerator. Do not freeze. Label with an expiration date of 3 months.

Rev. 08-2002M

Manufactured By
Atrix Laboratories, Inc.
Fort Collins, CO 80526

211-59

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-112

LABELING REVIEW(S)

ANDERSON

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

ANDA Number: 65-112

Date of Submission: November 30, 2001

Applicant's Name: Atrix Laboratories, Inc.

Established Name: Erythromycin and Benzoyl Peroxide Topical Gel USP, 3%-5%.
[Erythromycin 3% - Benzoyl Peroxide 5% topical gel]

Labeling Deficiencies:

1. CONTAINER:

   a. Erythromycin: 0.8 g and 1.6 g

      i. Revise to read, "Net Wt. ___ grams active erythromycin".

      ii. Print the text, "Prior to ... erythromycin" in bold print and add the text **"TO THE PHARMACIST: IMPORTANT"** in bold uppercase print immediately prior to this statement.

      iii. Increase the prominence of the statement, **"Not for separate dispensing".**

   b. Erythromycin and Benzoyl peroxide topical gel: 23.3 g and 46.6 g

      i. Front panel

         A. Delete "———" and add the text,"Topical gel: erythromycin (3%), benzoyl peroxide (5%)" immediately beneath the established name.

         B. Add the text "Net Wt." prior to "___ grams (as dispensed)".

         C. Prior to the text, "After ... and fragrance" add the word **"Description -".**

         D. Indicate the percentage of alcohol. We refer you to 21 CFR 201.10(d)(2).

      ii. Side panel

         A. Increase the prominence of the text appearing on the side panel, [except the text, "KEEP ... CHILDREN"].

         B. Delete the extra spaces appearing in the text of the third paragraph.

2. CARTON: 23.3 g and 46.6 g

   i. See comments 1(b)(i)(A and D) under CONTAINER.

   ii. Side panels flaps: **TO THE PHARMACIST**

Print the text: **"room temperature ETHYL ALCOHOL (70%)"** in bold print.

iii. Side panel

Increase the prominence of the text printed on the side panel, [except the text, "KEEP ... CHILDREN"].

iv. When printing final print, indicate the location of the lot number and expiration date.

3. INSERT

a. TITLE

i. Delete " ——— " following the established name and add the text, "Topical gel: erythromycin (3%), benzoyl peroxide (5%)" between the established name and the **"Rx"** symbol.

ii. Immediately following the **"Rx"** symbol, add a red box with the following text printed in red:

PLEASE READ COMPLETE COMPOUNDING DIRECTIONS
NOTE: TAP UNTIL ALL POWDER FLOWS FREELY. ADD ETHYL ALCOHOL (70%) TO VIAL (TO THE MARK) AND **IMMEDIATELY** SHAKE/DISSOLVE **COMPLETELY.**

iii. Following the red box print **"For Dermatologist Use Only – Not for Ophthalmic Use"** in bold print and "Reconstitute Before Dispensing" in bold red print.

b. DESCRIPTION

i. Add "USP" following the established name in the first sentence.

ii. We note that you list ——————— in your component statement. However, it is not listed in your list of inactive ingredients in the DESCRIPTION section. Please comment.

c. HOW SUPPLIED

i. Revise to read as follows:

TO THE PHARMACIST: IMPORTANT – Prior to dispensing, tap ...

ii. In this section, we encourage you to include a statement indicating that a spatula is supplied for mixing the drug product.

Please revise your container labels and carton and insert labeling, as instructed above, and submit in final print.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes - http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

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

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 25	X		
Is this name different than that used in the Orange Book?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? No		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	
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? NO Issues for FTR: Innovator individually cartoned? YES Light sensitive product which might require cartoning? NO Must the package insert accompany the product? YES *RLD packages the drug product in a carton.	*		
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	
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	
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	
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?		X	
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?		X	
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.		X	
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.			

APPEARS THIS WAY ON ORIGINAL

NOTES/QUESTION TO THE CHEMIST

1. The firm indicates that there is approximately a —% overage of the active ingredient in their drug product. Is this appropriate? Yes, RLD includes —% overage.

2. DESCRIPTION section:

   a. The firm indicates that the erythromycin used in its drug product is produced from a strain of "*Saccharopolyspora erythraea*". Is this accurate? Yes, it is accurate based on the DMF Annual Report (5-5-01).

   b. _____ is listed in the firm's component statement. However, it is not listed in the list of inactive ingredients in the DESCRIPTION section. This is a labeling deficiency. _____ was used as a Fragrance.

3. CONTAINER:

   a. Does the firm's 0.8 g and 1.6 g erythromycin containers meet the USP specifications for a tight container? Satisfactory per chemistry review #2.

   b. Does the firm's erythromycin and benzoyl peroxide gel 23 g and 46.6 g containers meet the USP specifications for a tight container?

Meet the usp spec per review #2.

GK 9/13/02

FOR THE RECORD

1. Reference listed drug labeling model:

   Benzamycin ® Topical Gel (erythromycin-benzoyl peroxide topical gel)
   NDA 50-557/S-018/approved March 5, 1996 [insert labeling] and S-015 approved October 21, 1994 [S-015 provides for a revised statement **"TO THE PHARMACIST"** on the label and labeling].

2. The inactive ingredients listed in the DESCRIPTION section are not consistent with the firm's components statement. [See comment under DESCRIPTION].
   [Vol. B1.1, p. 374]

3. Marketing package size:

   NDA – 23.3 g and 46.6 g - (as dispensed)
   ANDA – 23. 3 g and 46.6 g - (as dispensed)

4. Storage recommendations:

   USP – Before mixing, preserve the erythromycin and the vehicle containing benzoyl peroxide in separate, tight containers. After mixing, preserve the mixture in tight containers.
   NDA – Prior to reconstitution, store at room temperature between 15° and 30°C (59° – 86°F)
   After reconstitution, store under refrigeration between 2° and 8° C (36° – 86° F). Do not freeze. Keep tightly closed. Keep out of the reach of children.
   ANDA – same as RLD

5. Manufacturing Facility

   Atrix Laboratories, Inc.
   Fort Collins, CO

   [Vol. B1.2, p. 545]

6. CONTAINER/CLOSURE:

   1 & 2 ounces - white ——————— jar with a white ribbed ——————— cap
   1 ounce – 2 ½" white ——————— spatula
   2 ounces – 3 ¼" white ——————— spatula

   [Vol. B. 1.3, p. 954]

7. Physical Appearance:

   Opaque white cream
   [Vol.B 1.3, p. 1094]

8. This is the first generic Erythromycin and Benzoyl Peroxide Topical Gel USP, [Erythromycin 3% - Benzoyl Peroxide 5% topical gel] drug product.

Date of Review: 6/21/02

Date of Submission: 11/30/01

Primary Reviewer:
Jacqueline Council, Pharm.D.

Date:

Acting Team Leader
Captain Lillie Golson

Date: 7/22/02

cc: ANDA: 65-112
DUP/DIVISION FILE
HFD-613/JCouncil/LGolson (no cc)
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Review

APPEARS THIS WAY
ON ORIGINAL

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

ANDA Number: 65-112

Date of Submission: August 7, 2002

Applicant's Name: Atrix Laboratories, Inc.

Established Name: Erythromycin and Benzoyl Peroxide Topical Gel USP, 3%/5%.
[Erythromycin 3% - Benzoyl Peroxide 5% topical gel]

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):
Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: Erythromycin: 0.8 g and 1.6 g;
Erythromycin (3%) and Benzoyl Peroxide (5%) topical gel: 23.3 g and 46.6 g
Satisfactory in FPL as of the August 7, 2002 submission [Vol. 3.1].

Carton Labeling: 23.3 g and 46.6 g (Erythromycin (3%) and Benzoyl Peroxide (5%) topical gel)
Satisfactory in FPL as of the August 7, 2002 submission [Vol. 3.1].

Professional Package Insert Labeling:
Satisfactory in FPL as of the August 7, 2002 submission, [Vol. 3.1, Rev. 08-2002M, Code 8071-1]

Revisions needed post-approval: (Firm provided commitment on 3/1/04 to change storage temp. phrase to read controlled room temp. (Store at 20-25C/68-77F) see USP at next printing. MO 3/2/04

1. CONTAINER- Erythromycin and Benzoyl Peroxide Topical Gel
   Increase the prominence of the strength of each active ingredient.
2. CARTON
   Increase the prominence of "Avoid .....Eyes".
3. INSERT
   Separate the section headings, "How Supplied" and "Compounding Directions". Relocate "Compounding Directions" after the table.

BASIS OF APPROVAL:

Patent Data – NDA 50-557

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
None	None	None	There are no unexpired patents for this product in the Orange Book Database.	N/A	None

Exclusivity Data– NDA 50-557

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Benzymacin® Topcial Gel
NDA Number: 50-557
NDA Drug Name: Benzamycin® (erythromycin-benzoyl peroxide topical gel)

NDA Firm: Dermik Labs
Date of Approval of NDA Insert and supplement #: 03/05/96 (S-018) and 10/21/94 (S-015)
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-sides
Basis of Approval for the Carton Labeling: side-by-sides
Other Comments:

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 25	X		
Is this name different than that used in the Orange Book?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? No		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	
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? NO Issues for FTR: Innovator individually cartoned? YES Light sensitive product which might require cartoning? NO Must the package insert accompany the product? YES *RLD packages the drug product in a carton.	*		
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	
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	
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	
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?		X	
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?		X	
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.		X	
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.			

NOTES/QUESTION TO THE CHEMIST: The following questions have been adequately answered by the chemist, Dr. Kang.

1. The firm indicates that there is approximately a — % overage of the active ingredient in their drug product. Is this appropriate?
   Yes, since the RLD includes — % overage.

2. DESCRIPTION section:

   a. The firm indicates that the erythromycin used in its drug product is produced from a strain of "*Saccharopolyspora erythraea*". Is this accurate? Yes

   b. ——— is listed in the firm's component statement. However, it is not listed in the list of inactive ingredients in the DESCRIPTION section. This is a labeling deficiency.
   ——— is a fragrance

3. CONTAINER:

   a. Does the firm's 0.8 g and 1.6 g erythromycin containers meet the USP specifications for a tight container? Yes

   b. Does the firm's erythromycin and benzoyl peroxide gel 23 g and 46.6 g containers meet the USP specifications for a tight container. Yes

FOR THE RECORD

1. Reference listed drug labeling model:

   Benzamycin ® Topical Gel (erythromycin-benzoyl peroxide topical gel)
   NDA 50-557/S-018/approved March 5, 1996; rev: 6/95 [insert labeling] and S-015 approved October 21, 1994 [S-015 provides for a revised statement **"TO THE PHARMACIST"** on the label and labeling].

2. The inactive ingredients listed in the DESCRIPTION section are consistent with the firm's components statement. [Vol. 1.1, p. 374]

   The applicant stated in their August 15, 2002 amendment that ——— is not included on their insert because it is the fragrance inactive ingredient. Atrix chooses to use the general term fragrance, as seen in the innovator's labeling. This has been confirmed by the listing of inactive ingredients for Benzamycin® in the drug product query component of COMIS. The chemist, Dr. Kang has also confirmed that ——— is a fragrance.

3. Marketing package size:

   NDA – 23.3 g and 46.6 g - (as dispensed)
   ANDA – 23. 3 g and 46.6 g - (as dispensed)

4. Storage recommendations:

USP – Before mixing, preserve the erythromycin and the vehicle containing benzoyl peroxide in separate, tight containers. After mixing, preserve the mixture in tight containers.
NDA – Prior to reconstitution, store at room temperature between 15° and 30°C (59° – 86°F)
After reconstitution, store under refrigeration between 2° and 8° C (36° – 86° F). Do not freeze. Keep tightly closed. Keep out of the reach of children.
ANDA – same as RLD

5. Manufacturing Facility

Atrix Laboratories, Inc.
Fort Collins, CO
[Vol. 1.2, p. 545]

6. CONTAINER/CLOSURE:

1 & 2 ounces - white ——— jar with a white ribbed ———
1 ounce – 2 ½" white ——— spatula
2 ounces – 3 ¼" white ——— spatula

[Vol. 1.3, p. 954]

7. Physical Appearance:

Opaque white cream
[Vol. 1.3, p. 1094]

8. This is the **first generic** Erythromycin and Benzoyl Peroxide Topical Gel USP, [Erythromycin 3% - Benzoyl Peroxide 5% topical gel] drug product.

Date of Review: 9/17/02 Date of Submission: 8/7/02

Primary Reviewer: Michelle Dillahunt Date: 9/18/02

Acting Team Leader Lillie Golson Date: 9/18/02

cc: ANDA: 65-112
DUP/DIVISION FILE
HFD-613/MDillahunt/LGolson (no cc)
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Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-112

CHEMISTRY REVIEW(S)

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. CHEMIST'S REVIEW NUMBER
1

2. ANDA NUMBER
65-112 (First generic)

3. NAME AND ADDRESS OF APPLICANT

Atrix Laboratories, Inc.
Attention: Chris L. French
2579 Midpoint Drive
Fort Collins, CO 80525-4417

Telephone: 970-482-5868 Ext. 373 Fax: 970-482-9735

4. LEGAL BASIS for ANDA SUBMISSION
The basis of Atrix's proposed ANDA for Erythromycin-Benzoyl Peroxide Topical Gel USP, 3%;5% is the reference listed drug, Benzamycin® owned by Dermik Laboratories NDA 50-557. The applicant certifies that according to the information published in the list of Approved Drug Products 20th Ed, there is no exclusivity for the reference listed drug (V. 1.1, p. 7). The applicant certifies that according to the best of their knowledge, United States patent No. 4,387,107 by Dermik Laboratories expired on June 7, 2000 (V. 1.1, p. 8).

5. SUPPLEMENT(s)
None

6. PROPRIETARY NAME OF DRUG
None

7. NONPROPRIETARY NAME
Erythromycin-Benzoyl Peroxide Topical gel USP, 3%;5%.

8. SUPPLEMENT(s) PROVIDE(s) FOR
None

9. AMENDMENTS AND OTHER DATES

November 30, 2001	Original submission
January 10, 2001	New Correspondence

10. PHARMACOLOGICAL CATEGORY
Topical treatment for acne vulgaris.

11. HOW DISPENSED

Prescription

12. RELATED IND/NDA/DMF(s)

Product	Holder	DMF No.	LOA
[redacted]	[redacted]	[redacted]	V 1.3, p 1364
			V 1.3, p1352
			N/A

See section 37 for other related DMF's.

13. DOSAGE FORM

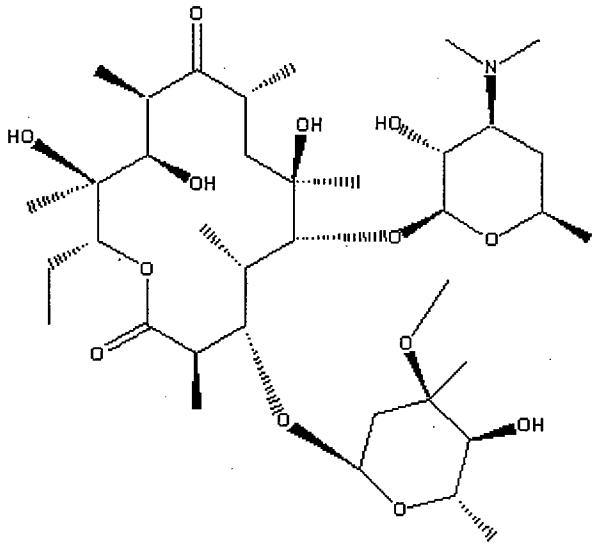
Gel

14. POTENCY

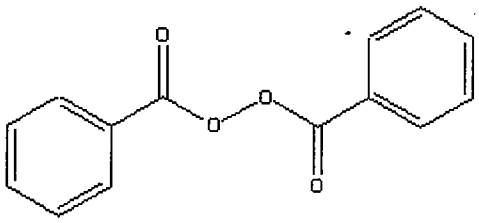
3%;5%

15. CHEMICAL NAME AND STRUCTURE

Erythromycin, CAS No. 114-07-8; $C_{37}H_{67}NO_{13}$, MW. 733.9352



Benzoyl peroxide, MW. 242.2306, CAS 94-36-0, $C_{14}H_{10}O_4$



16. RECORDS AND REPORTS

None

17. COMMENTS

The following sections are not satisfactory: Components and composition, Synthesis, Raw Material Controls, Container/Closure, Laboratory Controls, and Stability. The bioequivalency and labeling reviews are pending. The overall establishment inspection results are also pending.

18. CONCLUSIONS AND RECOMMENDATIONS

The application is not approvable [MINOR AMENDMENT].

19. REVIEWER AND DATE COMPLETED

Ramesh Sood/February 12, 2002; Revised, 2/27/02

APPEARS THIS WAY
ON ORIGINAL

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information from

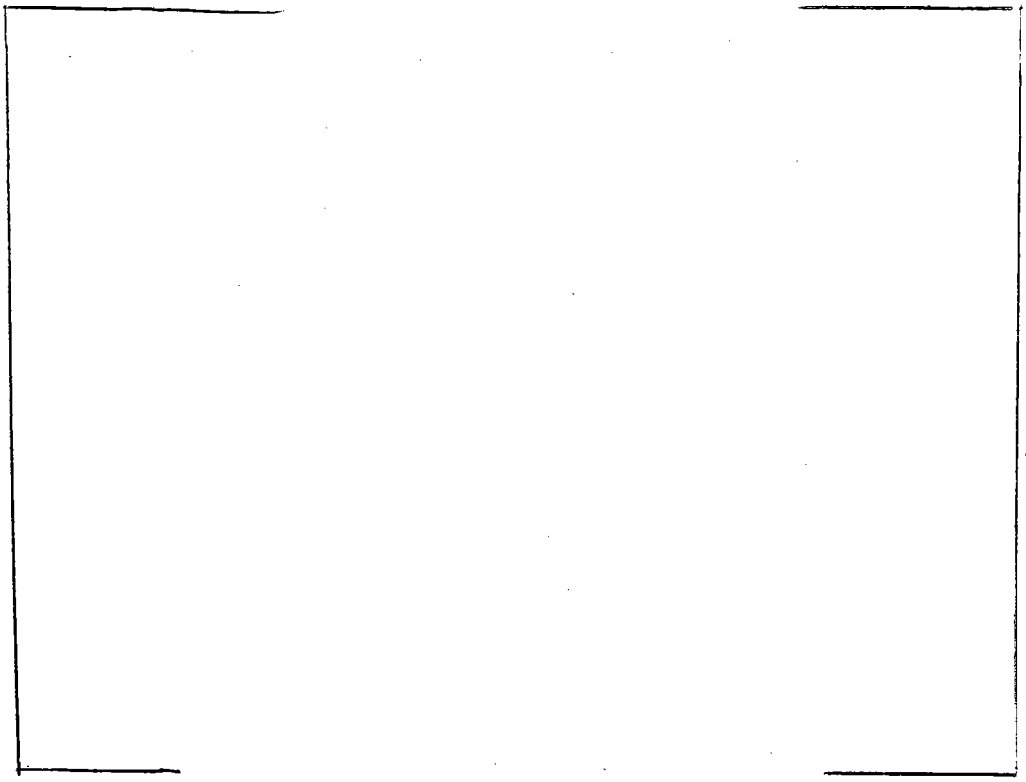
CHEMISTRY REVIEW #1

14.

15.

16.

17.



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

1. Please submit all available long-term stability data.

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

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

4. All facilities referenced in the ANDA must have a satisfactory compliance evaluation at the time of

approval. We have requested the necessary evaluation from the Office of Compliance.

Sincerely yours,

Paul Shuren for 3/13/02

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

APPEARS THIS WAY
ON ORIGINAL

cc: ANDA 65-112
Division File
Field Copy

Endorsements:

HFD-620/Ramesh Sood, Ph.D./2/27/02 RKS 3/7/02
HFD-620/J. Fan/3/4/02 3/8/02
HFD-617/S. Ho/3/7/02 3/8/02

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F/T by: DJ 3/7/02

OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. CHEMIST'S REVIEW NUMBER

2

2. ANDA NUMBER

65-112 (First generic)

3. NAME AND ADDRESS OF APPLICANT

Atrix Laboratories, Inc.
Attention: Chris L. French
2579 Midpoint Drive
Fort Collins, CO 80525-4417

Telephone: 970-482-5868 Ext. 373 Fax: 970-482-9735

4. LEGAL BASIS for ANDA SUBMISSION

The basis of Atrix's proposed ANDA for Erythromycin-Benzoyl Peroxide Topical Gel USP, 3%;5% is the reference listed drug, Benzamycin® owned by Dermik Laboratories NDA 50-557. The applicant certifies that according to the information published in the list of Approved Drug Products 20th Ed, there is no exclusivity for the reference listed drug (V. 1.1, p. 7). The applicant certifies that according to the best of their knowledge, United States patent No. 4,387,107 by Dermik Laboratories expired on June 7, 2000 (V. 1.1, p. 8).

5. SUPPLEMENT(s)

None

6. PROPRIETARY NAME OF DRUG

None

7. NONPROPRIETARY NAME

Erythromycin-Benzoyl Peroxide Topical Gel USP, 3%;5%.

8. SUPPLEMENT(s) PROVIDE(s) FOR

None

9. AMENDMENTS AND OTHER DATES

November 30, 2001	Original submission
January 10, 2002	New Correspondence
March 14, 2002	Deficiency letter based on the review #1
June 19, 2002	Minor amendment (Chemistry)
August 7, 2002	Amendment (Labeling)
September 30, 2002	Telephone amendment
October 14, 2002	Telephone amendment

10. PHARMACOLOGICAL CATEGORY

Topical treatment for acne vulgaris.

11. HOW DISPENSED

Prescription

12. RELATED IND/NDA/DMF(s)

Product	Holder	DMF No.	LOA
			V 1.3, p 1364
			V 1.3, p1352
			N/A

See section 37 for other related DMF's.

13. DOSAGE FORM

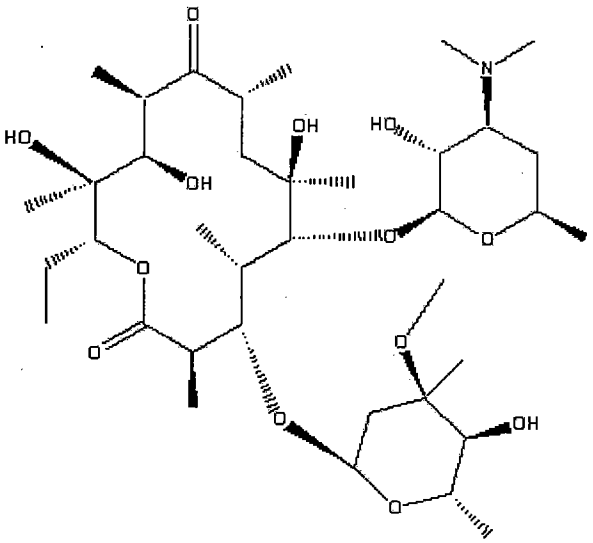
Gel

14. POTENCY

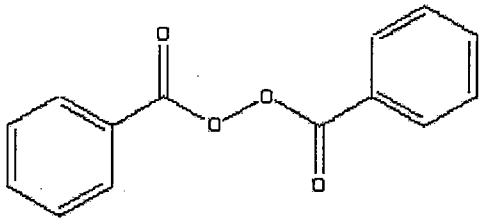
3%;5%

15. CHEMICAL NAME AND STRUCTURE

Erythromycin, CAS No. 114-07-8; $C_{37}H_{67}NO_{13}$, MW. 733.9



Benzoyl peroxide, MW. 242.2 CAS 94-36-0, $C_{14}H_{10}O_4$



16. RECORDS AND REPORTS

None

17. COMMENTS

Chemistry and labeling reviews are acceptable. EER is also acceptable. Not appovable due to Bioequivalency review.

18. CONCLUSIONS AND RECOMMENDATIONS

Not approvable due to bioequivalency review.

19. REVIEWER AND DATE COMPLETED

Gil Kang/November 7, 2002 Revised August 21, 2003

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information from

CHEMISTRY REVIEW #2

cc: ANDA 65-112
Division File
Field Copy

Endorsements:

HFD-620/G. Kang, Ph.D./11/8/02 NNfor G.K 8/21/03
HFD-620/J. Fan, TL/11/13/02 for, G/K 8/21/03
HFD-617/S. Ho, PM/ for 8/21/03

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OFFICE OF GENERIC DRUGS

ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. CHEMIST'S REVIEW NUMBER

3

2. ANDA NUMBER

65-112 (First generic)

3. NAME AND ADDRESS OF APPLICANT

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

Telephone: 970-212-4901 Fax: 970-482-9734

4. LEGAL BASIS for ANDA SUBMISSION

The basis of Atrix's proposed ANDA for Erythromycin-Benzoyl Peroxide Topical Gel USP, 3%;5% is the reference listed drug, Benzamycin® owned by Dermik Laboratories NDA 50-557. The applicant certifies that according to the information published in the list of Approved Drug Products 20th Ed, there is no exclusivity for the reference listed drug (V. 1.1, p. 7). There are no patents nor exclusivity listed in the "Orange Book".

5. SUPPLEMENT(s)

None

6. PROPRIETARY NAME OF DRUG

None

7. NONPROPRIETARY NAME

Erythromycin-Benzoyl Peroxide Topical Gel USP, 3%;5%.

8. SUPPLEMENT(s) PROVIDE(s) FOR

None

9. AMENDMENTS AND OTHER DATES

November 30, 2001	Original submission
January 10, 2002	New Correspondence
March 14, 2002	Deficiency letter based on the review #1
June 19, 2002	Minor amendment (Chemistry)
August 7, 2002	Amendment (Labeling)
September 30, 2002	Telephone amendment
October 14, 2002	Telephone amendment
August 26, 2003	NA letter based on the review #2 (Bio deficiency)
November 5, 2003	Formal dispute resolution request by Atrix
February 23, 2004	Amendment

March 1, 2004	Labeling commitment (Insert)
March 15, 2004	Telephone amendment (24-month stability data)
March 16, 2004	Telephone amendment (Corrections)
March 19, 2004	Telephone amendment (Stability specifications)

10. PHARMACOLOGICAL CATEGORY

Topical treatment for acne vulgaris.

11. HOW DISPENSED

Prescription

12. RELATED IND/NDA/DMF(s)

Product	Holder	DMF No.	LOA
			V 1.3, p 1364
			V 1.3, p1352
			N/A

See section 37 for other related DMF's.

13. DOSAGE FORM

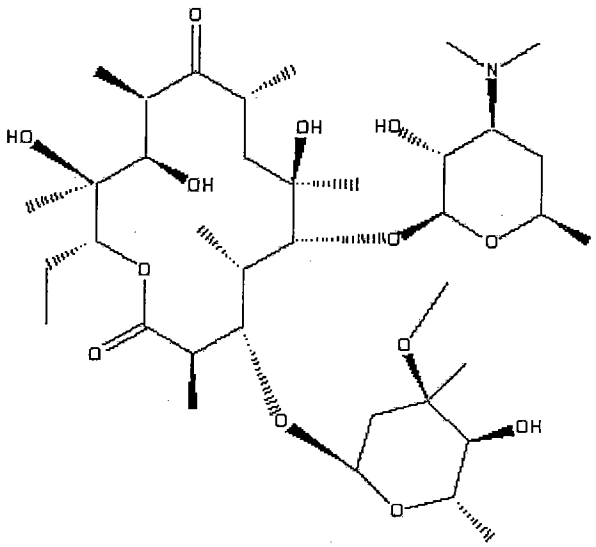
Gel

14. POTENCY

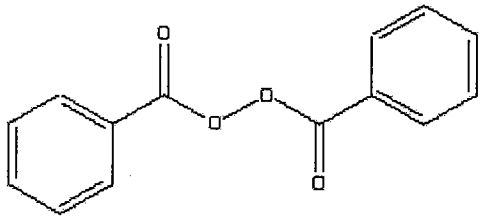
3%;5%

15. CHEMICAL NAME AND STRUCTURE

Erythromycin, CAS No. 114-07-8; $C_{37}H_{67}NO_{13}$ MW. 733.9



Benzoyl peroxide, CAS 94-36-0; $C_{14}H_{10}O_4$ MW. 242.2



16. RECORDS AND REPORTS

None

17. COMMENTS

-Bioequivalency is acceptable on 10-MAR-2004.

-The firm submitted 24-month stability data for delayed use on 15-MAR-2004 & 16-MAR-2004.

[redacted]

18. CONCLUSIONS AND RECOMMENDATIONS

Approvable

19. REVIEWER AND DATE COMPLETED

Gil Kang/March 24, 2004

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information from

CHEMISTRY REVIEW #3

cc: ANDA 65-112
Division File
Field Copy

Endorsements:

HFD-620/G. Kang, Ph.D./ GK 3/24/04
HFD-620/J. Fan, TL/ 3/24/04
HFD-617/A. Vu, PM/

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F/T by:

Approvable

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-112

BIOEQUIVALENCE REVIEW(S)

65-112
A2.1

Review of a Bioequivalence study with Clinical Endpoint

AUG 12 2003

ANDA: 65-112
Drug Product: Erythromycin-Benzoyl Peroxide Topical Gel USP
Sponsor: Atrix Laboratories
Reference Listed Drug: Benzamycin® Topical Gel, Dermik Laboratories, Inc., NDA #50557
Reviewer: Carol. Y. Kim, Pharm.D.
Submission dates: 11/30/01, 4/29/02
Date of Review: August 8, 2003
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I. Introduction

Benzamycin® Topical Gel

Benzamycin® Topical Gel is indicated for the topical treatment of acne vulgaris. This topical gel contains 3% erythromycin and 5% benzoyl peroxide. Erythromycin is a bacteriostatic agent and acts by inhibition of protein synthesis in susceptible organisms. Benzoyl peroxide is an antibacterial and keratolytic agent. Benzoyl proxide has been shown to be effective *in vitro* against *Propionibacterium acnes*, an anaerobe found in sebaceous follicles and comedones.

Acne Vulgaris

Acne vulgaris is a common skin condition that can affect people of all ages, although teenagers develop acne most often. About 10 to 20% of adults may continue to experience some form of the disorder that occurs when there is increase in sebum release by sebaceous glands. Small cysts, called comedones, form in hair follicles due to blockage of the follicular orifice by retention of sebum and keratinous material.

The clinical hallmark of acne vulgaris is the comedone, which may be closed (whitehead) or open (blackhead). Closed comedones are the precursors of inflammatory lesions of acne vulgaris and the contents are not easily expressed. Open comedones rarely result in inflammatory acne lesions and are filled with easily expressible oxidized, darkened, oily debris. Comedones are usually accompanied by inflammatory lesions: papules, pustules, or nodules. The most common location for acne is the face, but involvement of the chest and back is not uncommon.

II. Background

- The Sponsor previously submitted a protocol (#00-024) for review by the Office of Generic Drugs (OGD). On August 1, 2000, the OGD Associate Director for Medical Affairs, Dr. Fanning, completed the protocol review and issued the following comments to the Sponsor:

  A. The usual duration of studies for acne is 12 weeks and the usual endpoint is evaluated after 12 weeks of therapy.

B. Exclusion Criteria

5. Patients who are using any **prescribed** anti-inflammatory or immunosuppressive drugs (steroid nose drops and/or eye drops are permitted) as of the Baseline visit.

   A washout period for these products should be specified.

6. Patients who are using over-the-counter analgesics or anti-inflammatory drugs that are ingested in quantities **exceeding label instructions** as of the Baseline visit and throughout the study.

   *While the use of these over-the-counter analgesic and anti-inflammatory products **exceeding label instructions** should be an obvious exclusion, the more important definition should be the amount of use that would be permitted prior to and during the study. It is recommended that chronic use (with a specific definition) be inserted in the exclusion criteria and that use be limited to occasional (once again defined) during the study.*

C. A Physician's Global Assessment should be completed at each visit using a standardized scale to compare the change in severity of the dermatologic examination of acne to that at baseline.

D. The handling of patient discontinuation from the study needs to be better defined a priori. For example, the definition of poor compliance, at least the criteria as a minimum, and the definition of excluded medication use that is considered "acceptable" or "unacceptable" needs to be described more precisely.

E. Study Endpoints

1. The recommended clinical endpoint for an acne vulgaris study is usually 12 weeks of therapy.
2. The recommended primary efficacy measurements are 1) lesion counts **and** 2) Investigator 's Global Assessment.
3. Lesion counts should be presented as follows for inflammatory, non-inflammatory, and total lesions: 1) Baseline and Endpoint lesion counts, 2) mean reduction in lesion counts from baseline to endpoint, and 3) mean percentage reduction in lesion counts from baseline to endpoint.

F. The analysis populations should be defined in the protocol and should include an Intent-to-Treat population and an Evaluable population. The Evaluable population should be used for comparing equivalence of the active products and the intent-to-Treat population should be used for evaluating efficacy of the active products compared to the placebo.

G. A 90% confidence interval of 80-120% should be used in the bioequivalence comparison and a Yate's continuity correction performed. The 80-125% interval is used for the log comparisons in bioequivalence studies that assess Cmax and AUC and is not

used for bioequivalence studies with clinical endpoints that are not expressed as log variables. In order for a product to be considered bioequivalent, the two active products must be shown to be bioequivalent by the criteria outlined above and both active treatments must be shown to have greater efficacy than the vehicle control for the same endpoints.

- NDA 50-769 (11/27/00): For approval of the innovator's recent topical product, Benzamycin® Pak, which is very similar to the reference product but requires mixing prior to use, Benzamycin® Pak was compared to the reference product, Benzamycin® Topical Gel. According to the medical officer's review, Benzamycin® Pak was approved based on the outcome of mean percent reductions in all lesion counts (inflammatory, non-inflammatory, and total) and investigator's global assessment after 8 weeks of treatment. In four-arms study (#9708), Benzamycin® Pak vs. Benzamycin® Topical Gel vs. the corresponding vehicle formulations, the assessment of non-inferiority was performed against the active topical gel. The lower bounds of the 97.5% confidence interval for mean differences in all lesion counts (inflammatory, non-inflammatory, and total) were on and above –20% of the active topical gel. The investigator's global assessment was also within the lower bound of 97.5% CI. Benzamycin® Pak applied twice daily for 8 weeks was significantly more effective than vehicle and comparable to Benzamycin® Topical Gel.

III. Study Information

Protocol Number: BEN0002

The review of the protocol is included below with revisions to the original protocol in italics.

Title: A *12-week*, multi-center, double-blind, randomized, parallel study comparing Benzamycin® Topical Gel (Dermik Laboratories, Inc.), Erythromycin-Benzoyl Peroxide Topical Gel USP (Atrix Laboratories, Inc.), and Vehicle Control for the treatment of Acne Vulgaris.

Study Objectives:

1. To determine if Erythromycin-Benzoyl Peroxide Topical Gel USP (Atrix Laboratories, Inc.) is therapeutically equivalent to Benzamycin® Topical Gel by comparing the percent reduction from baseline in the numbers of inflammatory, non-inflammatory, and total lesions, and categorical improvement in Physician's Global Assessments. The primary time-point for determination of effectiveness was the Day 84 (planned end of treatment) visit.

2. To determine if Erythromycin-Benzoyl Peroxide Topical Gel USP (Atrix Laboratories, Inc.) and Benzamycin® Topical Gel are significantly different from the test product vehicle when comparing the percent reduction from baseline in the numbers of inflammatory, non-inflammatory, and total lesions, and categorical improvement in Physician's Global Assessments.

3. To compare the incidence of signs and symptoms in the 3 treatment groups.

Study Design: A prospective, randomized, multi-center, double-blind, vehicle-controlled, parallel group clinical study in which patients were randomized to one of the following 3 treatment groups in a ratio of 2:2:1:

1. Erythromycin-Benzoyl Peroxide Topical Gel USP (Atrix Laboratories, Inc.) twice daily for 12 weeks, *Lot #1304*,
2. Benzamycin® Topical Gel (Dermik Laboratories, Inc.) twice daily for 12 weeks, *Lot #MN5054*, or
3. Vehicle Control (placebo) (Atrix Laboratories, Inc.), *Lot #1308 and #1329*, twice daily for 12 weeks.

The three topical gels had the same approximate formulation.

Study Population

Study subjects were both male and female patients, 12 years of age and older. Female patients were not pregnant or nursing, and, if sexually active, must be either sterile, post-menopausal, or using an acceptable method of birth control.

Inclusion Criteria

- Signed informed consent;
- Male and female patients, *12 years* of age or older;
- Female patients, not pregnant or breastfeeding, practicing appropriate birth-control;
- Female patients 55 years of age or younger require a negative pregnancy test or proof of surgical sterilization or post-menopausal status;
- Must be in good physical and mental health;
- Must be willing to avoid "sunburn" of the treated skin by excessive exposure to natural or artificial sunlight (e.g. tanning devices);
- Must be willing to avoid swimming for 2 hours following test article application;
- Must have a clear diagnosis of moderate to moderately severe acne vulgaris of the face, as defined by having >/= 15 inflammatory acne lesions (pustules and papules), >/=10 comedones (non-inflammatory acne lesions), and </= 3 nodules above the mandibular line at Baseline.

Exclusion Criteria

- Patients with a history of systemic cancer therapy in the last 5 years and/or radiation therapy of the head and/or neck at any time;
- Patients with a cancer diagnosis without a history of stability/remission for greater than 5 years, with the exception of non-metastatic basal and/or squamous cell carcinomas of the skin. Enrollment into the study of patients with basal and/or squamous cell carcinomas should be discussed with the Atrix Study Director on a case-by-case basis;

- Patients with uncontrolled asthma or asthma requiring regular use of asthma medications as defined by >/= 3 times per week;
- Patients who have been diagnosed with any immunological disorder such as HIV or systemic lupus erythematous;
- Patients who have used any prescribed anti-inflammatory or immunosuppressive drugs (steroid nose drops and/or eye drops are permitted) *within two weeks prior to the Baseline visit;*
- Patients who have used over-the-counter analgesics or anti-inflammatory drugs that were ingested in quantities exceeding label instructions. *Intermittent use of label indicated amount of drug is acceptable during the study. Chronic use following Baseline visit is not acceptable;*
- Patients who have used topical drugs, (especially topical acne treatment products[e.g., antibiotics, topical vitamin A derivatives such as Retin=A]), medicated cosmetics or cleansers anywhere on the body, within two weeks prior to Baseline and throughout the study;
- Patients who have received systemic medication or therapy within the four weeks prior to Baseline or throughout the study known to affect acne or inflammatory responses, including but not limited to: antihistamines, antibiotics(especially erythromycin), megadoses of vitamin A, hormones (excluding those used for birth control), spironolactone (aldactone, aldactizide), cyproterone acetate, etc.;
- Patients who have received isotretinoin (Accutane ®) within the six months prior to Baseline or throughout the study;
- Patients who have used clindamycin anywhere on the body, within two weeks prior to Baseline and throughout the study;
- Patients who have any medical condition which, in the investigator's judgement, makes the patient ineligible or places the patient at undue risk (e.g., pancreatitis, liver or kidney disease/failure, systemic infection, anemia, agranulocytosis, or peripheral neuropathy);
- Patients who have damaged skin (excluding acne) on the face which includes excessive scars, excessive hair including a beard, or other disfiguration on the face that would obscure the acne evaluation;
- Patients with severe cystic acne or acne conglobata;
- Patients who have changed their make-up or moisturizers within the 30 days prior to Baseline or throughout the study, excluding lipstick;
- Patients who have a history of clinically significant heart disease;
- Patients with a known allergy to one of the ingredients in the test article as follows: erythromycin, benzoyl peroxide, carbomer —, ethyl alcohol, docusate sodium, sodium hydroxide, ————————;
- Patients with a known hypersensitivity to the sun or having been sunburned on the face or neck within the 21 days prior to baseline;
- Patients who have participated in any type of investigative study within the 30 days prior to Baseline or throughout the study;
- Female patients who have started a new, or having changed their current oral contraceptive, contraceptive implant, or Depo Provera™ injection within four months prior to Baseline visit.

Randomization/Blinding

Patients were randomly assigned to a treatment group by a computer-generated table. An individual at each site who was not involved in safety or efficacy evaluations prepared the product. Patients, Investigators, and Atrix clinical personnel who performed the dermatological evaluation were blinded to study treatments.

Study Procedures

Baseline

Following evaluation of inclusion and exclusion criteria, eligible patients must sign an informed consent agreement. Obtaining medical history, physical examination, use of concomitant medications, dermatological examination, *Global Acne Assessment*, lesion counts, and pregnancy testing for women less than 56 years were completed at the baseline visit. The study medication was dispensed with instructions.

Weeks 2, 4, 6, and 8 Evaluation

The use of concomitant medications, occurrence of adverse events, and compliance were recorded. A dermatological examination, acne lesion count, and the Global Acne Assessment were performed. For Global Acne Assessment, the following scale was used:

Global Acne Assessment

0.0	*Facial skin need not be perfectly clear. A few comedones or papules may be present, but these should be visible only on close examination.*
1.0	*Comedones and small papules are present and noticeable from a distance of 1-3 ft away.*
2.0	*About one fourth of facial area is involved, with small papules (about 6 to 12) comedones (a few pustules or large prominent papules may be present.*
3.0	*Approximately 30% (26-49%) of facial area is involved with small papules (13 to 20) and small comedones (a few pustules or large prominent papules may be presented).*
4.0	*Approximately half of facial area is involved, with small papules and large or small comedones. A few pustules or large prominent papules are usually present.*
5.0	*More than half (51-74%) of facial area is involved with large and small papules and comedones (lesser facial area of involvement is permissible if inflammatory lesions are large). A moderate number of pustules is usually present, some of which may be large.*

6.0	*Approximately three fourths of facial area is involved, with papules and/or large open comedones. Numerous pustules are usually present, some of which may be large.*
7.0	*Greater than 75% but less than 85% of facial area is involved with lesions with the majority being papules and large open comedones. Pustules may be large and prominent.*
8.0	*Practically all of facial area is involved with lesions. Large prominent pustules are usually visible. Lesions are usually highly inflammatory. Other types of acne (such as conglobata, including sinus and systic types) may be present.*

Week 10

The use of concomitant medications, occurrence of adverse events, and compliance were recorded. *No dermatological examination or assessment was performed at this visit.*

Week 12 (or Premature Termination)

The use of concomitant medications, occurrence of adverse events, and compliance were recorded. A dermatological examination, acne lesion count, and global acne assessment were completed. A brief physical examination was also performed. All female patients who required a pregnancy test at baseline performed another pregnancy test. Prior to patient dismissal, all items have been checked for completion.

Criteria for Discontinuation of Patients

Patients could voluntarily elect to discontinue their participation in the study at any time. The Investigators were responsible for removing a subject from the study if they determined that it was in the patient's best interest. This included discontinuation for medical reasons or failure to comply with required study conduct, such as poor compliance, use of excluded medications, or failure to comply with instructions given. *If a patient missed greater than 2 consecutive days or greater than 5 days of total treatment application, or failed to keep appointments, the patient was considered as failed to follow the procedure of the study.*

Variations from the scheduled visit days were defined in the protocol as follows: 1) Week 2 visit could vary by +/- 24 hours, and 2) Week 4, 6, 8, 10 and *12 visits* could vary by +/- 48 hours.

Analysis

The Sponsor used the following three populations for the analyses:

I) The Safety population consisted of all patients randomized to receive study drugs.

II) The Intent-to-Treat (ITT) population met all inclusion criteria and had at least one application of the study drug. This population was used for the superiority comparisons of the two active

treatments to the Vehicle Control. Missing visit data were supplied by the Last Observation Carried Forward (LOCF) method.

III) The Per Protocol (PP) population (Efficacy-Evaluable population) included patients who had completed all visits required by the protocol or excluded any patient from the intent-to-treat dataset which may have been compromised based upon the evaluability criteria described in the protocol. For efficacy evaluation, missing patient's data were excluded. The LOCF method was not applied.

Although the required visit window for the Week 12 (Day 84) was initially proposed in the protocol as +/– 2 days, the sponsor applied +/– 4 days in the efficacy-evaluable analysis based on review of other similar acne studies.

The efficacy-evaluable population was used for demonstrating bioequivalence and the intent-to-treat population was used for the measures of superiority. The primary efficacy endpoints were assessed with the mean percent change from baseline in inflammatory lesions (papules, pustules, and nodules) and the Physician's Global Assessment at Day 84 (week 12).

The secondary endpoints were proposed as the following:

- Mean reduction-from-baseline for all lesion counts [inflammatory (IF), non-inflammatory (NIF) and total (IF and NIF)];
- Mean percentage reduction in lesion counts for non-inflammatory and total lesions;
- Mean lesion counts for all lesion types (IF, NIF, and total);
- Mean Global Acne Assessment score;
- Mean reduction-from-baseline for Global Acne Assessment score.

The analysis was performed using ANOVA incorporating the following factors in the model: treatment group, center, treatment-by-center interaction, and baseline lesion count. If the treatment-by-center interaction or baseline lesion terms were not statistically significant, they were removed from the model. The subgroup analyses of age, race and gender were not conducted. For the clinical bioequivalence comparison, a 90% confidence interval was used with two one-sided t-tests (α=0.05). For the superiority comparisons, Dunnett's test was used to compare the active treatments to the Vehicle Control.

Reviewer's Comments: *In previous communication (protocol #00-024) with this sponsor, the OGD medical officer recommended that the primary efficacy is measured by the lesion counts and investigator's global assessment. The medical officer further specified that lesion counts should be presented for all lesions including inflammatory, non-inflammatory, and total. For data analysis, it was recommended to tabulate 1) baseline and endpoint lesion counts, 2) mean reduction in lesion counts from baseline, and 3) mean percentage reduction in lesion counts from baseline.*

Benzamycin® Topical Gel is indicated for the topical control of acne vulgaris, which consists of both inflammatory and non-inflammatory lesions. In the review of NDA 50-769, all three lesion

counts were considered for the evaluation of efficacy for the approval of the innovator's Benzamycin® Pak. To demonstrate the bioequivalence of two products for the treatment of acne vulgaris, all lesion counts (inflammatory, non-inflammatory, and total) should be considered as the primary endpoints in addition to investigator's global assessment.

IV. RESULTS

Based on the OGD request, the sponsor submitted the study amendment (4/29/02) providing a list of patients for each population analysis.

Study period: 2/2/01-7/18/01

Study centers: 13 sites

Site #	Investigator	Address
1	MD	
2	MD	
3	MD	
4	MD	
6	MD	
7	MD	
8	MD	
10	MD	
11	, MD	
12	, MD	
	, MD	
14	MD	
15	MD	

Study Enrollment:

A total of 352 patients were enrolled into the study with 140 randomized to Atrix's Erythromycin-Benzoyl Peroxide Topical Gel USP, 142 to Benzamycin® Topical Gel, and 70 to the vehicle arm. The distribution of patients in the three analysis populations is summarized in Table I. The distribution of patients in each analysis population at each study site is shown in Table II. Since the sponsor did not provide reasons for exclusions under each analysis populations, this reviewer summarized the sponsor's study report based on data submitted in vol. 1.2 and vol. 1.3. The sponsor excluded additional subjects (n=44) who had not been evaluated with the same examiner at all time points.

Table 1
Distribution of Patients in the Three Analysis Populations (per reviewer)

Population	Total	Test	Reference	Vehicle
Safety	352	140	142	70
Without on-study data	-13	-2	-6	-5
ITT	339	138	136	65
Didn't complete week 12				
Exclusion 1 (for week 2 and week 4)	2	0	-1	-1
Exclusion 2	9	-3	-3	-3
Exclusion 3	1	-1	0	0
Exclusion 4	2	-1	-1	0
Exclusion 6	5	-4	0	-1
Exclusion 7	6	-1	-3	-2
Exclusion 8	3	-1	0	-2
Exclusion 9	6	-1	-2	-3
Exclusion 10	1	0	-1	0
Completed but were excluded from the analysis				
Exclusion 1 (at week 12 visit)	23	-9	-11	-3
Exclusion 2	11	-6	-3	-2
Exclusion 3	14	-4	-5	-5
Exclusion 4	2	0	-2	0
Exclusion 5	25	-10	-12	-3
Exclusion 6	18	-7	-6	-5
Exclusion 11	3	-1	-2	0
PP included in the final analysis	208	89	84	35

Reasons for Exclusion:

1=outside visit window only ($\geq \pm 4$ day) 2=non-compliance only (NC)
3=prohibited medication use only 4=Adverse event only (ADE)
5=not evaluated by the same examiner at all time points only (NSE)
6=any combination of NC, outside visit window, prohibited medication use, or NSE
7=voluntary withdrawal 8=lack of effect
9=lost to follow-up 10=other (moved out of area)
11=no clear acne diagnosis

Table II
Distribution of Subjects in Analysis Populations at Study Sites (per reviewer)

Site #	Investigator	SAFETY				ITT				PP			
		Test	Ref	Veh	Total	Test	Ref	Veh	Total	Test	Ref	Veh	Total
1		10	10	5	25	10	10	4	24	7	5	4	16
2		14	14	7	35	14	13	7	34	8	8	4	20
3		12	12	6	30	12	11	5	28	9	9	3	21
4		10	10	5	25	9	8	4	21	8	8	4	20
6		14	14	7	35	14	14	6	34	11	11	4	26
7		8	9	4	21	8	9	3	20	8	9	3	20
8		11	12	5	28	11	12	5	28	8	12	4	24
10		10	10	5	25	10	9	5	24	9	9	3	21
11		7	8	4	19	7	7	4	18	4	2	2	8
12		13	12	7	32	13	12	7	32	12	11	5	28
13		10	10	5	25	10	10	5	25	9	10	5	24
14		10	10	5	25	10	10	5	25	4	5	4	13
15		11	11	5	27	10	11	5	26	10	10	4	24
Total		**140**	**142**	**70**	**352**	**138**	**136**	**65**	**339**	**107**	**109**	**49**	**265**

Reviewer's Comments:

Based on the protocol, the sponsor excluded patients taking any antibiotic treatment from both safety and efficacy analyses. Although patients taking any antibiotic treatment should be excluded from the efficacy analysis, these patients should be included in the safety evaluation.

Demographics

Of the 352 patients enrolled in the study, 180 (51%) were male and 172 (49%) were female. The mean age was 18.8 (range 12-54). The majority of patients were Caucasian (72%). The other racial groups were represented as follows: Black , 20%, Hispanic, 16%, Asian, 8%, and Other, 6%. The demographics of PP population were similar across centers.

Baseline Disease

The lesion counts at baseline for subjects in the ITT and PP populations were similar in each treatment group and are presented in Table III. Statistical analysis among the treatment arms with respect to the number of baseline lesions was not performed.

Table III

Inflammatory, Non-Inflammatory, and Total Lesions at Baseline in Each Treatment Group (SE)

Lesions	Intent-to-treat Population			Per Protocol Population		
	Test	Reference	Vehicle	Test	Reference	Vehicle
N	138	136	65	107	109	49
Inflammatory	35.7 (1.9)	34.0 (1.8)	29.5 (2.2)	36.1 (2.2)	34.6 (2.2)	30.0 (2.8)
Non-Inflammatory	36.6 (2.6)	41.0 (3.0)	42.0 (4.4)	36.2 (3.0)	39.2 (2.5)	41.4 (4.8)
Total Lesions	72.4 (3.3)	75.0 (3.5)	71.4 (5.1)	72.3 (3.8)	73.8 (3.4)	71.3 (5.4)

Compliance

The Sponsor reported that Compliance was measured at Day 0 (baseline), 14, 28, 42, 70, and 84. Compliance determination was made based on a patient missing 3 consecutive test article applications or six total applications between study visits. The number of subjects who did not complete the study due to non-compliance was the same in both test and reference groups (4-Test; 4-Reference).

Efficacy

The sponsor's analysis of percent change from baseline for inflammatory, non-inflammatory, and total lesion counts and the Physician's Global Assessment for the Day 84 visit are shown in Table IV and Table V. The ITT population is used for comparison of the vehicle to each of the active drug products. The Per Protocol population is used for the comparison of the test and reference products.

The mean percent change from baseline of the lesion counts (Day 84) and the Physician's Global Assessment (Day 84) for the ITT population is presented in Table IV.

Table IV
Mean Percent Change from Baseline of Lesion Counts and Physician's Global Assessment (Day 84) for the ITT Population (SE): Sponsor's data

Variable	Test	Reference	Vehicle	p-value*
Mean % change from baseline in lesion counts (SE)	N = 138	N = 136	N = 65	-
Inflammatory	47.7 (3.3)	53.0 (3.3)	33.9 (4.8)	Test vs. Veh: <0.05
				Ref vs. Veh: <0.05
Non-inflammatory	25.8 (4.8)	20.2 (4.8)	18.2 (6.9)	Test vs. Veh: NS
				Ref vs. Veh: NS
Total	38.5 (3.0)	39.4 (3.0)	25.4 (4.3)	Test vs. Veh: <0.05
				Ref vs. Veh: <0.05
Physician's Global Assessment	41.5 (2.7)	46.9 (2.7)	30.1 (3.9)	Test vs. Veh: <0.05
				Ref vs. Veh: <0.05

*NS: not significant; no p-value was provided in the report

Reviewer's comments: *The active products showed statistically significant improvement in inflammatory and total lesion counts compared to vehicle control group at the end of the 12-week treatment (Day 84). For non-inflammatory lesion counts, both the test and reference products did not show statistically significant improvement compared to the vehicle control group. The Sponsor did not provide actual p-values for comparison.*

The mean percent change from baseline of the lesion counts (Day 84) and the Physician's Global Assessment (Day 84) for the Per Protocol population is presented in Table V.

Table V
Mean Percent Change from Baseline of Lesion Counts and Physician's Global Assessment (Day 84) for the Per Protocol Population (SE): per Sponsor

Variable	Test	Reference	90% CI
Mean % change from baseline (SE)	N= 89	N = 84	-
Inflammatory	53.0 (4.0)	53.6 (4.2)	0.817; 1.161
Non-inflammatory	25.0 (5.7)	19.5 (5.6)	**0.606; 1.960**
Total	41.2 (3.6)	38.3 (3.8)	**0.858; 1.292**
Physician's Global Assessment (PGA)	45.1 (3.0)	47.8 (3.1)	0.800; 1.087

Reviewer's Comment: *The sponsor compared the mean percent change from baseline for all lesion counts at Day 84 for the evaluable population and computed 90% confidence intervals for the test and the reference products. According to their analysis, the test and reference products failed to show that they are equivalent. They do not meet 90% confidence interval criteria of (0.80, 1.25) except for Inflammatory lesion counts. Both Non-inflammatory and Total lesion counts did not fall within acceptable confidence interval criteria for bioequivalence. For topical*

acne products indicated for the treatment of acne vulgaris, the percent change from baseline in all lesion counts should fall within the confidence interval criteria to demonstrate bioequivalence. Furthermore, superiority of the active treatment products over the vehicle should be demonstrated for the ITT population to show the sensitivity of the equivalence test. The FDA statistician was consulted for reanalysis and verification of the sponsor's data.

For demonstration of bioequivalence with Physician's Global Assessment (PGA), the sponsor used mean percent score change from baseline. This is not acceptable to the OGD. The OGD recommends the evaluation of PGA to be dichotomized into "success" and "failure" categories. Using the sponsor's definition of Global Acne Assessment on a scale of 0 to 8, a score of 0 (facial skin need not be perfectly clear; a few comedones or papules may be present, but these should be visible only on close examination) is considered as treatment success. A score above zero should be considered as treatment failure. In NDA #50769 (Benzamycin® Pak), a score of zero or 0.5 on a scale of 0 to 4[1] was considered as treatment success.

The primary endpoints evaluated by the OGD are mean percent reduction from baseline in all lesion counts and the Physician's Global Assessment. The mean numerical lesion counts, and mean numerical reduction from baseline for all lesion counts (inflammatory, non-inflammatory, and total) are considered as secondary endpoints. These data are presented in Tables VI and VII.

Table VI
Primary Endpoints (per sponsor)

1. Mean percent reduction from baseline

A. ITT Populations

Inflammatory

Variable	Test	SE	Ref	SE	Vehicle	SE
D14	32.9	2.6	30.1	2.6	14.3	3.8
D28	41.4	2.7	38.7	2.7	21.4	4.0
D42	49.6	2.7	45.8	2.7	25.5	4.0
D56	54.4	2.9	47.8	2.9	23.5	4.2
D84	47.7	3.3	53.0	3.3	33.9	4.8

Non-inflammatory

Variable	Test	SE	Ref	SE	Vehicle	SE
D14	18.5	3.4	10.9	3.4	6.8	4.9
D28	22.6	5.4	8.5	5.4	8.1	7.8
D42	24.1	5.4	16.5	5.4	12.4	7.8
D56	25.1	4.9	17.4	5.0	8.0	7.1
D84	25.8	4.8	20.2	4.8	18.2	6.9

[1] PGA score of 0=clear, no inflammatory lesions; 0.5=sparse comedones, with very few or no inflammatory lesions present

Total

Variable	Test	SE	Ref	SE	Vehicle	SE
D14	27.0	2.1	21.8	2.1	11.3	3.0
D28	33.1	2.4	28.3	2.4	14.7	3.4
D42	37.3	2.6	35.7	2.6	20.1	3.7
D56	38.5	2.6	37.2	2.6	16.8	3.8
D84	38.5	3.0	39.4	3.0	25.4	4.3

B. PP Populations

Inflammatory

Variable	Test	SE	Ref	SE
D14	32.5	3.3	28.7	3.3
D28	43.4	3.0	37.6	3.1
D42	51.3	3.2	43.8	3.3
D56	53.2	3.9	46.4	4.0
D84	53.0	4.0	53.6	4.2

Non-inflammatory

Variable	Test	SE	Ref	SE
D14	13.1	4.1	7.4	4.1
D28	21.4	4.9	14.4	5.1
D42	22.9	4.2	23.1	4.3
D56	27.0	6.0	18.4	6.3
D84	25.0	5.7	19.5	5.6

Total

Variable	Test	SE	Ref	SE
D14	24.3	2.6	19.2	2.7
D28	33.3	2.7	27.7	2.8
D42	37.9	3.1	34.6	3.2
D56	40.9	3.4	36.3	3.5
D84	41.2	3.6	38.3	3.8

2. Physician's Global Assessment

	Mean Assessment Scores (ITT Population)						Mean Assessment Scores (PP Population)			
Variable	Test	SE	Ref	SE	Veh	SE	Test	SE	Ref	SE
D14	3.38	0.07	3.42	0.07	3.73	0.10	3.40	0.08	3.37	0.08
D28	3.00	0.08	3.04	0.08	3.55	0.11	3.02	0.09	3.04	0.09
D42	2.69	0.09	2.82	0.09	3.37	0.13	2.72	0.11	2.91	0.11
D56	2.59	0.09	2.59	0.09	3.33	0.13	2.53	0.12	2.50	0.13
D84	2.50	0.10	2.23	0.11	3.03	0.15	2.38	0.12	2.212	0.13

Table VII
Secondary Endpoints (per sponsor)

1. Mean numerical lesion counts (MLC) and Mean numerical lesion count reduction from baseline (MRB)

A. ITT Population

Inflammatory

	MLC						MRB					
Variable	Test	SE	Ref	SE	Veh	SE	Test	SE	Ref	SE	Veh	SE
D14	21.03	0.94	22.97	0.95	28.40	1.37	12.79	0.94	10.85	0.95	5.42	1.37
[illegible]	19.07	0.98	19.64	0.98	25.46	1.42	14.75	0.98	14.18	0.98	8.36	1.42
[illegible]	16.29	0.95	17.83	0.95	22.66	1.38	17.53	0.95	15.99	0.95	11.16	1.38
D56	16.06	1.00	16.25	1.00	23.34	1.45	17.76	1.00	17.57	1.00	10.48	1.45
D84	16.96	1.17	15.52	1.18	20.02	1.70	16.86	1.17	18.30	1.18	13.80	1.70

Non-Inflammatory

	MLC						MRB					
Variable	Test	SE	Ref	SE	Veh	SE	Test	SE	Ref	SE	Veh	SE
D14	33.17	1.25	34.01	1.25	37.72	1.81	6.22	1.25	5.38	1.25	1.67	1.81
D28	31.94	1.56	31.92	1.57	38.12	2.26	7.45	1.56	7.47	1.57	1.27	2.26
D42	32.29	1.76	28.46	1.77	35.58	2.55	7.10	1.76	10.93	1.77	3.81	2.55
D56	31.16	1.81	28.29	1.82	37.19	2.62	8.23	1.81	11.10	1.82	2.21	2.62
D84	29.79	1.73	27.80	1.74	32.60	2.51	9.61	1.73	11.59	1.74	6.79	2.51

Total

	MLC						MRB					
Variable	Test	SE	Ref	SE	Veh	SE	Test	SE	Ref	SE	Veh	SE
D14	53.65	1.69	56.94	1.70	66.82	2.45	19.57	1.69	16.27	1.70	6.39	2.45
D28	50.19	2.15	51.52	2.17	64.62	3.13	23.02	2.15	21.69	2.17	8.59	3.13
D42	47.62	2.30	46.29	2.332	59.44	3.34	25.59	2.30	26.93	2.32	13.77	3.34
[illegible]	46.25	2.43	44.54	2.45	61.75	3.53	26.96	2.43	28.67	2.45	11.46	3.53
[illegible]	45.92	2.48	43.31	2.50	53.66	3.60	27.29	2.48	29.90	2.50	19.56	3.60

B. PP Population

Inflammatory

	MLC				MRB			
Variable	Test	SE	Ref	SE	Test	SE	Ref	SE
D14	22.68	1.20	24.50	1.21	12.50	1.20	10.68	1.21
D28	19.10	1.08	21.02	1.11	16.54	1.08	14.62	1.11
D42	16.84	1.10	18.32	1.14	18.01	1.10	16.53	1.14
D56	16.35	1.37	16.87	1.42	19.45	1.37	18.93	1.42
D84	14.82	1.13	14.44	1.18	19.39	1.13	19.77	1.18

Non-Inflammatory

	MLC				MRB			
Variable	Test	SE	Ref	SE	Test	SE	Ref	SE
D14	33.35	1.35	34.53	1.36	3.98	1.35	2.80	1.36
D28	30.49	1.52	31.54	1.56	7.67	1.52	6.62	1.56
D42	30.12	1.45	28.17	1.50	7.44	1.45	9.40	1.50
D56	27.44	1.57	26.79	1.63	9.63	1.57	10.28	1.63
D84	27.27	1.71	27.79	1.79	9.85	1.71	9.34	1.79

Total

	MLC				MRB			
Variable	Test	SE	Ref	SE	Test	SE	Ref	SE
D14	55.82	1.87	59.45	1.88	16.68	1.87	13.06	1.88
D28	49.41	2.19	53.05	2.26	24.39	2.19	20.75	2.26
D42	46.45	2.21	46.42	2.29	25.97	2.21	26.00	2.29
D56	43.28	2.46	43.92	2.55	29.59	2.46	28.95	2.55
D84	41.27	2.41	42.73	2.51	30.06	2.41	28.60	2.51

3. Mean numerical lesion counts (MLC) and Mean numerical lesion count reduction from baseline (MRB) at Day 84

Variables		Test	SE	Reference	SE	CI
Inflammatory	MLC	14.82	1.13	14.44	1.18	0.845, 1.207
	MRB	19.39	1.13	19.77	1.18	0.849, 1.113
Non-inflammatory	MLC	27.27	1.71	27.79	1.79	0.839, 1.124
	MRB	9.85	1.71	9.34	1.79	0.631, 1.479
Total	MLC	41.27	2.41	42.73	2.51	0.836, 1.096
	MRB	30.06	2.41	28.60	2.51	0.857, 1.245
Global Acne Assessment	Mean assessment Score	2.38	0.12	2.21	0.13	0.949, 1.206
	Mean reduction in assessment score	1.83	0.12	2.00	0.13	0.772, 1.057

Reviewer's comments on efficacy endpoint

Subgroup Analysis of age, race or gender was not performed by the Sponsor.

Safety Evaluation

Adverse events

The sponsor reported a total of 262 adverse events in the study. Of 252 adverse events, 122 patients experienced adverse events, 52 (128 events) in the test group, 47 (96 events) in the reference group, and 23 (38 events) in the vehicle group. The most common adverse events are listed in Table VIIIa. Most adverse events were mild to moderate, with only 14 reported to be severe (not treatment related). The treatment related adverse events at the application site for the test, reference and vehicle groups were 22, 16, and 4, respectively. Ten types of skin related adverse events were reported. Of all that affected the skin, application site dryness was the most frequent event and reported in 3-6% of patients in both active treatment groups similar to the incidence reported in labeling for Benzamycin® Pak. Since the sponsor's data did not correspond to the data listings that accompany the study report, the reviewer tabulated its findings in Table VIIIb.

Table VIIIa (per Sponsor)

Analysis of treatment-related adverse events (fisher exact test)						
Severity	Mild		Moderate		Mild	Moderate
Event	Test N=140	Reference N=142	Test N=140	Reference N=142	Test vs. Ref	Test vs. Ref
Application site dryness	5	4	4	0	N/S	N/S
Application site reaction NOS (erythema)	1	3	3	0	N/S	N/S

N/S=not significant

APPEARS THIS WAY
ON ORIGINAL

Table VIIIb (per reviewer)

Adverse Events (AE)	Test	Reference	Vehicle
All AEs (N)	**155**	**108**	**38**
Mild	**87**	**76**	**29**
Moderate	**59**	**27**	**9**
Severe	**9**	**5**	**0**
Systemic			
Headache	13	11	4
Nasopharyngitis	9	12	5
AE Related to Study Treatments (Skin)			
Application site of Skin			
Dryness	8	5	1
Reaction NOS	3	3	1
Burning	2	2	0
Pruritus	2	2	0
Edema	2	0	0
Rash	1	1	0
Irritation	1	0	0
Paraesthesia	0	1	0
Pigmentation changes	1	0	0
Injury to skin			
Sunburn	2	2	2

Reviewer's comments:

1. *The sponsor reported that five patients (14 events) experienced serious adverse events. Of these patients, one patient (#06272, reference) was hospitalized due to worsening of sickle cell anemia, and one patient (#07309, reference) became pregnant during the study. Three patients (#1055, #14293, #15256) from the test group discontinued the study due to mild to moderate skin related adverse events (facial dryness, peeling, erythema) at the application site and the sponsor considered all of them as serious adverse events.*

2. *The sponsor included a pregnant woman in the efficacy analysis. Due to protocol violation, this patient's data should be excluded from per protocol population analysis.*

3. *More moderate and severe adverse events were reported for the test vs. the reference product. However, they were considered not related to the study treatments.*

Concomitant Medications:

Concomitant medications were taken by 189 patients. The most common concomitant medications were anti-depressants, analgesics, cold remedy, contraceptives, anti-histamines, and

anti-inflammatory agents. Fourteen patients (4-Test, 5-Reference, 5-Vehicle) who completed the 12-week course of study were excluded from the per protocol population analysis due to short-term use of antibiotics lasting 7-10 days.

V. Formulation

Atrix's Erythromycin-Benzoyl Peroxide Gel is packaged with two different sub-components. The first component is erythromycin active packaged separately as powder. The second component is Benzoyl peroxide gel containing inactive ingredients. A pharmacist is instructed to mix these two components prior to dispensing.

Ingredients	% w/w
Erythromycin USP	3%
Benzoyl Peroxide	5%
Carbomer —, NF	
Alcohol	
Docusate Sodium	
Sodium Hydroxide, NF	
Purified Water, USP	

The Regulatory Branch review indicates that all inactive ingredients are acceptable for filing. (vol. 1.1.)

VI. Findings of DSI inspection report

Two of the 13 sites from this study have been previously inspected for Clay-Park's Ammonium Lactate Cream (ANDA 75-774) and both sites were classified VAI - voluntary action indicated due to minor retention sample issue. Based on Clay-Park's explanation and additional documentation, the bioequivalence data conducted at these sites were accepted for the approval. Therefore, the decision was made not to inspect the clinical sites of Atrix's ANDA 65-112 on February 4, 2003.

VII. Findings of Statistical Review (7/17/03)

According to the FDA statistical review, patient #13155 (reference) was excluded from the evaluable population analysis due to violation of the inclusion criteria. The minimum number of lesion count required for the study is 15 inflammatory lesions but this patient had 14 inflammatory lesion count. With this modification, the total of 207 patients (T: 89, Ref: 83, P: 35) were included in the final evaluable population. For determination of bioequivalence, the FDA statistician used two different analyses, Rank Transformation and Proportional Odds Ratio (see statistical review for details of statistical methods).

Since the efficacy of the innovator's recent product, Benzamycin® Pak was evaluated following 8 weeks of treatment, this reviewer requested the FDA statistician to evaluate week 8 data in

addition to week 12 data. Based on the FDA statistical review, the sponsor failed to show that the test product is bioequivalent to the reference product at either week 8 or week 12. Consistent with the sponsor's reported data, the percent reduction from baseline fell within the bioequivalence limits only for inflammatory lesions. Percent reduction for non-inflammatory and total lesions failed to meet the bioequivalence criteria.

Both test and reference products demonstrated superiority over vehicle for percent reduction of inflammatory and total lesion counts, but not for non-inflammatory lesions. See below for the summary of the FDA statistician's data.

Table 1: Equivalence Analysis (percent change from baseline) – global acne assessment and lesion counts (raw and rank values) for the EFF population at week 12 (extracted from statistical review)

	Raw				***Rank***	
variable	Test LS mean	Ref. LS mean	90% Confidence Interval (%)	Pass/Fail	90% Confidence Interval (%)	Pass/Fail
Global acne assessment	**45.35**	**46.82**	**83.1, 112.9**	**P**		
Inflammatory lesion	**53.67**	**53.68**	**84.1, 119.0**	**P**	**93.4, 115.5**	**P**
Non-inflammatory lesion	24.92	20.40	67.6, 247.0	F	88, 153	F
Total lesion	41.16	39.02	85.9, 130.3	F	92, 128	F

Table 2: Efficacy analysis (percent change from baseline) – global acne assessment and lesion counts (raw and rank values) for the ITT population at week 12 (extracted from statistical review)

	Test vs. placebo			Ref. vs. placebo		
Variable	Test Drug LS Mean	Placebo LS Mean	p-value	Ref. Drug LS Mean	Placebo LS Mean	p-value
Raw						
Global acne assessment	**41.33**	**30.01**	**0.020**	**46.77**	**30.64**	**<0.001**
Inflammatory lesion	**47.73**	**33.22**	**0.019**	**53.18**	**34.00**	**<0.001**
Non-inflammatory lesion	25.84	18.58	0.331	23.65	17.51	0.444
Total lesion	38.49	25.36	0.015	39.76	25.56	0.005
Rank						
Inflammatory lesion	**111.54**	**82.10**	**<0.001**	**111.94**	**78.86**	**<0.001**
Non-inflammatory lesion	108.15	92.56	0.066	105.03	89.44	0.069
Total lesion	111.24	85.17	0.002	109.15	83.23	0.002

Consistent with the findings at week 12, the percent change from baseline in all lesion counts at week 8 did not show bioequivalency between the test and the reference products. Percent reduction from baseline fell within the 90% confidence interval only for inflammatory lesions

using Rank analysis. Both the test and the reference products were shown to be superior to vehicle in all lesion counts for Rank values, but not for Raw analysis.

Therefore, either at week 8 or week 12, the sponsor failed to demonstrate bioequivalence between the test and reference products.

The Physician Global Assessment evaluation should be considered as a dichotomous variable for evaluation of bioequivalence, using a score of 0 for treatment success and a score of 1 or above as treatment failure. For the PP population, 10/89, 7/83, and 2/35 number of patients were considered as treatment success at week 12 in the test, reference, and vehicle, respectively. For the ITT population, 14/137, 12/133, and 3/65 number of patients were considered as treatment success at week 12 in the test, reference, and vehicle, respectively. Based on this reviewer's analysis, the 90% confidence interval of the proportional difference in the treatment success between the test and the reference products at week 12 for the evaluable population was (-0.058, 0.11), which is within the accepted bioequivalence limits of (–0.20, +0.20). Both active treatment groups showed improvement over the vehicle group.

VIII. Conclusion

The data presented in this ANDA failed to demonstrate that Atrix Laboratories, Inc.'s Erythromycin-Benzoyl Peroxide Topical Gel USP, 3%, 5%, is bioequivalent to the reference listed drug, Benzamycin® Topical Gel. The FDA statistical review confirms that the percent reduction from baseline in all lesion counts (inflammatory, non-inflammatory, and total) at week 12 did not fall within the 90% confidence interval limits of (0.80, 1.25).

IX. Recommendation

The data submitted to ANDA 65-112 failed to demonstrate bioequivalence of Atrix Laboratories, Inc.'s Erythromycin-Benzoyl Peroxide Topical Gel USP, 3%, 5%, with the reference listed drug, Benzamycin® Topical Gel, using the accepted primary endpoint of percent reduction from baseline in all lesion counts (inflammatory, non-inflammatory, and total) at week 12 and the dichotomized (success/failure) analysis of the Physician Global Assessment.

Considering that a previous NDA for erythromycin-benzoyl peroxide topical gel was approved with 8-week studies, the 8-week data in this application was also analyzed, and it also failed to meet the accepted bioequivalence criteria.

Whereas the comedone (non-inflammatory lesion) is a clinical hallmark of acne vulgaris, products are not approved for this indication without demonstrating effectiveness for both inflammatory and non-inflammatory lesions, and it is therefore important for a generic formulation to demonstrate effectiveness within the bioequivalence limits for both lesion types.

Carol Y. Kim

8/8/03

Carol Y. Kim, Pharm.D.
Clinical Reviewer
Office of Generic Drugs

Date

Dena R. Hixon MD

8/12/03

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

Date

for Barbara M. Davit

8/12/03

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs

Date

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA:65-112 APPLICANT:Atrix Laboratories, Inc.

DRUG PRODUCT: Erythromycin-Benzoyl Peroxide Topical Gel, USP 3%, 5%

The Division of Bioequivalence has completed its review and the following deficiencies have been identified:

The data submitted to ANDA 65-112 failed to demonstrate bioequivalence of Atrix Laboratories, Inc.'s Erythromycin-Benzoyl Peroxide Topical Gel USP, 3%, 5%, with the reference listed drug, Benzamycin® Topical Gel, using the accepted primary endpoint of percent reduction from baseline in all lesion counts (inflammatory, non-inflammatory, and total) at week 12 and the dichotomized (success/failure) analysis of the Physician Global Assessment.

Considering that a previous NDA for erythromycin-benzoyl peroxide topical gel was approved with 8-week studies, the 8-week data in this application was also analyzed, and it also failed to meet the accepted bioequivalence criteria.

Whereas the comedone (non-inflammatory lesion) is a clinical hallmark of acne vulgaris, products are not approved for this indication without demonstrating effectiveness for both inflammatory and non-inflammatory lesions, and it is therefore important for a generic formulation to demonstrate effectiveness within the bioequivalence limits for both lesion types.

Sincerely yours,

for Barbara M. Davit

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

CC: ANDA 65-112
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-600/ C.Kim
HGD-600/ D. Hixon

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Endorsements: (Final with Dates)
HFD-600/C. Kim
HFD-600/D. Hixon
for HFD-650/D. Conner

BIOEQUIVALENCY - UNACCEPTABLE

submission date:
November 30, 2001
April 29, 2002

1. Bioequivalence Study (STU)

Strengths: 3%, 5%
Outcome: UC

2. Study Amendment (STA)

Strengths: 3%, 5%
Outcome: UC

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

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA:65-112 APPLICANT:Atrix Laboratories, Inc.

DRUG PRODUCT: Erythromycin-Benzoyl Peroxide Topical Gel, USP 3%, 5%

The Division of Bioequivalence has completed its review and the following deficiencies have been identified:

The data submitted to ANDA 65-112 failed to demonstrate bioequivalence of Atrix Laboratories, Inc.'s Erythromycin-Benzoyl Peroxide Topical Gel USP, 3%, 5%, with the reference listed drug, Benzamycin® Topical Gel, using the accepted primary endpoint of percent reduction from baseline in all lesion counts (inflammatory, non-inflammatory, and total) at week 12 and the dichotomized (success/failure) analysis of the Physician Global Assessment.

Considering that a previous NDA for erythromycin-benzoyl peroxide topical gel was approved with 8-week studies, the 8-week data in this application was also analyzed, and it also failed to meet the accepted bioequivalence criteria.

Whereas the comedone (non-inflammatory lesion) is a clinical hallmark of acne vulgaris, products are not approved for this indication without demonstrating effectiveness for both inflammatory and non-inflammatory lesions, and it is therefore important for a generic formulation to demonstrate effectiveness within the bioequivalence limits for both lesion types.

Sincerely yours,

Barbara M Davit

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

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 65-112 SPONSOR : Atrix Laboratories

DRUG AND DOSAGE FORM : Erythromycin and Benzoyl Peroxide Topical Gel USP

STRENGTH(S) : 3%/5%

TYPES OF STUDIES : Clinical endpoint

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic ___ New facility _____ For cause ____ Other ____	Inspection requested: (date) Inspection completed: (date)	

ASSOCIATE DIRECTOR FOR MEDICAL AFFAIRS, OGD : DENA R. HIXON, M.D.

INITIAL : DRH DATE : 3/10/04

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm.D.

INITIAL : DPC DATE : 3/8/04

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:65-112 APPLICANT:Atrix Laboratories, Inc.

DRUG PRODUCT: Erythromycin-Benzoyl Peroxide Topical Gel, USP 3%, 5%

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

The data submitted to ANDA 65-112 are adequate to demonstrate bioequivalence of Atrix Laboratories, Inc.'s Erythromycin-Benzoyl Peroxide Topical Gel USP, 3%, 5%, with the reference listed drug, Benzamycin® Topical Gel, using the primary endpoint of percent reduction from baseline in inflammatory lesion count at week 12.

1. The primary endpoints specified in your protocol are those upon which the approval of the reference product was based. Your study demonstrated equivalent performance of your product and the RLD for those endpoints and also demonstrated non-inferiority for percent reduction in non-inflammatory lesions, the additional endpoint currently used in the evaluation of acne vulgaris products.

2. Your study did not demonstrate superiority over placebo for either the test or reference product with regard to the Investigator's Global Assessment when analyzed as a dichotomous endpoint as recommended by the Division of Dermatologic and Dental Products (DDDDP), using a score of 0 at the end of treatment as the definition of success. However, DDDDP agrees that the more subjective Investigator's Global Assessment can be removed from the bioequivalence evaluation of topical acne vulgaris products.

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

14

MAR 9 2004

RESPONSE TO REQUEST FOR DISPUTE RESOLUTION

OGD#03-886

ANDA:	65-112
Drug Product:	Erythromycin-Benzoyl Peroxide Topical Gel USP
Sponsor:	Atrix Laboratories
Reference Listed Drug:	Benzamycin® Topical Gel, Dermik Laboratories, Inc., NDA #50557
Date of Original ANDA:	November 30, 2001
Date of ANDA Amendment:	February 23, 2004
Date of Formal Dispute Resolution Request (OGD#03-886):	November 4, 2003
Date of Review:	February 25, 2004

History of ANDA 65-112

ANDA 65-112 for Erythromycin-Benzoyl Peroxide Topical Gel USP was submitted by Atrix Laboratories, Inc. on 11/30/01 and received on 12/3/01. The application included a bioequivalence study with a clinical endpoint to establish bioequivalence between the generic and reference products. The review of that study dated August 8, 2003 found the study inadequate to demonstrate bioequivalence based on the study design and endpoints recommended by the Division of Dermatologic and Dental Drug Products (DDDDP) for evaluation of generic topical products for treatment of acne vulgaris.

DDDDP had recommended that a generic product for treatment of acne vulgaris should be superior to vehicle for percent change from baseline in at least two of the three lesion counts (inflammatory, non-inflammatory, and total lesions) and for success on the Physician's Global Assessment (PGA) after 12 weeks of treatment. DDDDP further recommended that equivalence be demonstrated for percent change from baseline in all three lesion counts and the PGA. Success on the PGA was to be defined as a score that is consistent with a state of clear or almost clear.

After reviewing the Summary Basis of Approval for the RLD, Atrix had submitted a draft protocol for review by the Office of Generic Drugs (OGD) on June 7, 2000. The proposed study would enroll up to 300 patients randomized in a 3:3:1 ratio to receive generic (test) drug, reference drug, or vehicle control for 10 weeks of treatment. Equivalence between the test and reference drug products was to be established if the ratio of the mean week 10 total inflammatory lesion count for the test treatment group to the reference treatment group fell within the standard confidence limit of 80 to 125%. The protocol included as secondary endpoints overall severity grade and the number of non-inflammatory and total lesions.

In the response to the proposed protocol, OGD recommended a 12-week study and recommended lesion counts and PGA as primary endpoints. The letter stated the following:

> Lesion counts should be presented as follows for inflammatory, non-inflammatory, and total lesions: 1) Baseline and Endpoint lesion counts, 2)

mean reduction in lesion counts from baseline to endpoint, and 3) mean percentage reduction in lesion counts from baseline to endpoint.

Atrix interpreted this to mean that the PGA was to be a primary endpoint in addition to their proposed primary endpoint of inflammatory lesions. They did not understand that the measurements they had considered secondary (non-inflammatory and total lesion counts) must also be within the established bioequivalence limits.

Atrix enrolled a total of 352 patients into their study, with 140 randomized to the generic product, 142 to Benzamycin, and 70 to the vehicle arm. Patients were required to have a clear diagnosis of moderate to moderately severe acne vulgaris of the face, as defined by having at least 15 inflammatory acne lesions and at least 10 non-inflammatory lesions and no more than 3 nodules. Average baseline lesion counts in the test, reference and vehicle arms, respectively, were 36, 34, and 30 inflammatory lesions, 37, 41, and 42 non-inflammatory, and 72, 75, and 71 total lesions.

Review of the study report submitted in ANDA 65-112 revealed that the sponsor had analyzed the PGA using a percent change from baseline, and not as a success proportion as recommended by DDDDP. This analysis had not been addressed in the protocol review by OGD. The sponsor's analysis of percent change from baseline showed that both the test and reference products were superior to vehicle ($p<0.05$) for inflammatory lesions, total lesions, and PGA but not for non-inflammatory lesions. The 90% confidence intervals of the test/reference ratios of the percent change from baseline were within the established limits of (0.80, 1.25) for inflammatory lesions and PGA but not for non-inflammatory or total lesions.

The OGD statistical review revealed that the data regarding percent change from baseline in lesion counts were significantly skewed, and rank transformation of the data was therefore used for the OGD statistical analysis. Using this analysis, OGD confirmed that the 90% confidence interval (CI) of the test/reference ratio of the percent change from baseline for inflammatory lesions was (0.934, 1.155), within the established bioequivalence limits. However, the CI for non-inflammatory lesions was (0.88, 1.53) and for total lesions was (0.92, 1.28), showing slightly better performance of the generic than of the reference product for these endpoints. Both test and reference products were superior to placebo ($p<0.05$) for inflammatory and total lesions, but not for non-inflammatory lesions.

Although the percent change from baseline for PGA was superior to placebo for both test and reference products, and the 90% CI was within established bioequivalence limits, this analysis is not consistent with the recommendations of DDDDP to analyze the difference success proportions between test and reference groups, using a definition of success as a PGA score consistent with a score of clear or almost clear.

Previous studies of Benzamycin Products

The original NDA 50-557 for Benzamycin Topical Gel was submitted 2/27/81. It included reports of five studies, including only two that used the formulation to be marketed and one additional study that involved only a difference in one inactive

ingredient. These 3 double-blind randomized studies included four groups of patients, treated with benzamycin gel, benzoyl peroxide gel, erythromycin gel, or placebo for 10 weeks. In each group, 16 to 22 patients with acne vulgaris grades III through VII (Cook et. al.) completed the studies. The reviewer stated, "The scores that I consider most significant for evaluation of efficacy are the reduction in comedone counts, the end-of-treatment reduction in papule + pustule counts (expressed as excellent, good, fair, or poor) and the end-of-treatment global evaluation of clinical response (expressed as moderate-to-excellent improvement, slight improvement, or no change-worse)." Percent reduction in inflammatory lesions and in non-inflammatory lesions was calculated, but was not evaluated for statistical significance. The reviewer concluded that benzamycin was effective in 2 of the 3 studies for reduction in non-inflammatory lesions and in all 3 studies for reduction of inflammatory lesions and the global evaluation. However, the studies failed to show a significant contribution of the erythromycin to the combination, and therefore the application was not approved.

A supplement was submitted to NDA 50-557 on 8/9/83 with the results of an additional study. In this study, 128 patients with acne vulgaris grade II or III (Pillsbury Classification) and a minimum of 5 and maximum of 10 lesions were randomized to the same four treatment arms as in the previous studies, 30 patients per group, for 10 weeks of treatment. The numbers of lesions (comedones, papules, pustules and cysts) were counted at each visit and the percent reduction from baseline determined. The sum of the inflammatory lesions was determined at each visit and an objective improvement scale based on this sum as follows: excellent = greater than 75% reduction from baseline, good = 50-75% reduction, fair = 25-50% reduction, poor = less than 25% reduction. A global evaluation was also made at the end of therapy using the following scale: worse, no change, slight improvement, moderate improvement, excellent improvement. The reviewer stated that the reductions in papule and pustule counts are the best indicators of clinical improvement in the evaluation of topical anti-microbial acne agents, and only percent reduction in inflammatory lesions was considered in the review. An outside expert consultant to the FDA performed a statistical analysis of the results and concluded that Benzamycin was superior to its ingredients in 2 of the 4 studies. The reviewer considered the results to be medically meaningful and appropriate, and the application was subsequently approved.

A subsequent NDA 50-769 was submitted 1/26/00 for Benzamycin Pak, also known as Benzamycin ———, and Benzamycin ———, a new formulation that was considered a line-extension product of the approved Benzamycin Gel product. This NDA included two clinical efficacy studies, one four-arm comparison of the ——— vs. Benzamycin vs. both vehicles, and a second study of Benzamycin ——— vs. ——— placebo, both with treatment duration of 8 weeks.

The first study enrolled a total of 327 patients with a minimum score of 1.5 on the global acne severity scale, at least 15 and no more than 80 facial inflammatory lesions, and at least 20 and no more than 140 facial comedones. Mean lesion counts for all patients at baseline were 55 comedones (range from 0 to 170), 27 inflammatory lesions (range 4 to 88), and 83 total lesions (range 24 to 235). Both active products were statistically

superior to placebo in both mean numerical reduction in lesion counts and mean percent reduction in lesion counts for all three lesion types (inflammatory, non-inflammatory and total) and in proportion of patients with success on the PGA, defined as a score of clear or almost clear (sparse comedones with very few or no inflammatory lesions present). In addition, the active dual pouch was found to be non-inferior to the active gel in lesion reduction with the lower bounds of the 97.5% confidence interval for mean differences all at or above the limit of -20% of the active topical gel. (Upper bounds were not provided in the review.)

The second study enrolled 223 patients with the same enrollment criteria as for the previous study and randomized them 1:1 to active or placebo treatment for 8 weeks. The lesion counts were 42 comedones (range 2 to 139), 30 inflammatory lesions (range 15 to 83), and 72 total lesions (range 23 to 192). The active treatment was superior to placebo for treatment success on the PGA and both numerical reduction from baseline and percent reduction in inflammatory and total lesion counts *but not for reduction in non-inflammatory lesions.*

Atrix Request for Dispute Resolution

Atrix points out that subsection 505(j) of the FDA Act is intended to simplify and speed approval of low cost generic drugs and that, therefore, the ANDA applicant must establish that the new drug is bioequivalent to the reference listed drug and that the generic manufacturer is not required to conduct human clinical trials to demonstrate safety and efficacy of the generic product.

Atrix concludes that FDA has the discretion to reach any of the following conclusions and approve ANDA 65-112, and that if FDA maintains that the Atrix product is not bioequivalent to the RLD, it should "cogently explain" how the basis for its decision is consistent with science, with agency precedent, and within the statute and agency policy to approve safe and effective lower cost generic drug products.

1. Atrix followed the advice of OGD and established the bioequivalency of their product to the RLD based on the primary endpoints identified in the RLD approval.
2. The requirement to show bioequivalence for the test drug to the reference drug, and also superiority for both the reference and test drug to the vehicle is unnecessary and contrary to the intent of Section 505(j)(2)(A) of the FDC Act.
3. Insistence on a confidence interval of 80% to 125% is unnecessary and inappropriate for a study with a parallel rather than a crossover study design.
4. Requiring that all measured endpoints be within the 80 to 125% confidence interval is unnecessary to establish bioequivalence when the approval of the RLD was based on effectiveness for inflammatory lesions only.
5. Evidence that the Atrix product is at least as good as the reference drug is consistent with agency precedent and established bioequivalence.
6. ANDA precedents for other topical products including acne drug products, in which clinical results act as "surrogates" for pharmacokinetic comparisons should have different "goal posts" for approval

7. A generic drug should not be held to a higher standard than is currently required for an innovator drug.

Discussion

Atrix believes that its study demonstrated bioequivalency and superiority based on principal endpoints predetermined in the protocol and consistent with FDA's advice. The study was designed based on the summary basis of approval for the RLD, which clearly emphasized the importance of *reduction in inflammatory lesions* for treatment of acne vulgaris. Furthermore, the study showed that the Atrix product is at least as good as Benzamycin for reduction of non-inflammatory lesions.

NDA 50-557 for Benzamycin Gel was evaluated according to a different standard than what is currently being applied in evaluation of new drug products for treatment of acne vulgaris. The original NDA was not evaluated for statistical superiority of Benzamycin over placebo for reduction in either inflammatory or non-inflammatory lesions, and the study groups were too small to have likely shown statistically significant differences. The current standard has required that a product indicated for treatment of acne vulgaris be statistically superior to placebo for percent reduction in two of the three lesion counts (inflammatory, non-inflammatory, and total lesions) and have a statistically larger success proportion for the PGA. However, it is recognized that the change in total lesion count will be strongly influenced by the change in the lesion type that shows the largest effect. Therefore, DDDDP is considering new guidelines for evaluation of these products that would require significant reduction in both inflammatory and non-inflammatory lesions, compared to placebo, and a significantly larger success proportion for the PGA, compared to placebo, with success defined *a priori* as either a score consistent with clear or almost clear or a reduction of at least 2 points from baseline on the PGA scale.

The review of NDA 50-557 reveals that all 3 of the original studies submitted in 1981 were interpreted as showing effectiveness for reduction in inflammatory lesions and moderate to excellent improvement on the global evaluation, but only 2 of the 3 studies were interpreted as showing effectiveness for reduction in non-inflammatory lesions. In the 1984 supplement, reduction in non-inflammatory lesions was not evaluated by the medical officer. All of these studies were too small to reach statistical significance for any endpoint by today's standards.

NDA 50-769 for Benzamycin Pak enrolled a similar number of patients compared to the Atrix study, with about three times as many patients in each active treatment arm compared to the original NDA studies. In NDA 50-769, both Benzamycin Gel and the new Benzamycin Pak formulation showed superiority over placebo for all endpoints, including both numerical reduction and percent reduction in inflammatory, non-inflammatory, and total lesion counts and success on the PGA. The only remarkable difference between the study populations for the Benzamycin Pak studies compared to the Atrix study was a higher baseline non-inflammatory lesion count in the Benzamycin Pak studies. The study demonstrated non-inferiority of Benzamycin Pak to Benzamycin Gel, whereas an ANDA for a generic product must meet both upper and lower equivalence limits to be approved under 505(j).

The second study conducted for NDA 50-769 enrolled a similar number of patients per arm and had baseline comedone counts more similar to the Atrix study, and it demonstrated superiority over placebo for PGA and for reduction in inflammatory and total lesions, *but not for reduction in non-inflammatory lesions*.

Given that Atrix based its study design on the Summary Basis of Approval for the reference product and that FDA did not clearly state that all three lesion types should be evaluated as primary endpoints, it is reasonable to conclude that Atrix was not given adequate advice to encourage enrollment of the optimum study population to demonstrate effectiveness and equivalence in reduction of non-inflammatory lesions.

As stated by Atrix, the intent of subsection 505(j) of the FDA Act is to simplify and speed approval of low cost generic drugs. The ANDA applicant must establish that the new drug contains the same active ingredient as the RLD and that it is bioequivalent (releases the active ingredient to the site of action at the same rate and extent). The only currently available means of establishing bioequivalence of a locally acting generic drug is by demonstrating equal effectiveness of the generic and reference drug for clinical endpoints for which the reference has already been shown to be effective. It is not consistent with the intent of subsection 505(j) to hold the generic to a higher efficacy standard than the reference product by requiring that it show efficacy for an endpoint for which the RLD did not clearly show efficacy. Therefore, the sponsor's argument for establishing bioequivalence of their erythromycin benzoyl peroxide gel to Benzamycin gel based on equivalent performance in reduction of inflammatory lesions and PGA is acceptable as long as the generic product does not cause a worsening of non-inflammatory lesion count. In this case, the study results showed that the 90% confidence interval of test/reference ratio of the percent change from baseline in non-inflammatory lesions fell above the established lower limit of 0.80, demonstrating that the test product is at least as good as the reference product for this endpoint.

It is noteworthy that Atrix analyzed the PGA using percent change from baseline instead of the success proportion that has been recommended by DDDDP. When re-analyzed as a success proportion, defining success as a score of 0 (consistent with a state of clear or almost clear), the 90% CI of the difference in success proportions between test and reference products meets the bioequivalence limits of (-0.20, +0.20). However, using this definition of success, the success proportion is small for both the generic and reference products, and neither the generic nor the reference product shows superiority over placebo. Given that the end-of-treatment global evaluation of clinical response in the original Benzamycin NDA studies was expressed as moderate-to-excellent improvement, slight improvement, or no change-worse, it is not reasonable to expect that either the generic or RLD should be superior to placebo for success proportion when success is defined as a state of clear or almost clear. While not a pre-defined endpoint in this case, if success is defined as a decrease of at least 2 points on the PGA scale compared to baseline (the alternate definite of success proposed by DDDDP for new acne vulgaris products), both generic and reference products are shown to be superior to placebo.

DDDDP continues to recommend that topical generic products for treatment of acne vulgaris show equivalent performance in reduction of both inflammatory and non-inflammatory lesion types. However, in a consultation dated 1/29/04, they state that the more subjective Investigator's Global analysis could be removed from the study to simplify future study design for drugs applying via 505(j) for the acne indication.

OGD does not agree that a generic product must show equivalent performance on an endpoint for which the RLD did not show superiority over placebo. In the study under consideration, both the Atrix product and Benzamycin met the current DDDDP criteria of statistical superiority over vehicle for percent reduction from baseline in two of the three lesion counts, inflammatory and total lesions, but did not show statistical superiority for the third lesion type, non-inflammatory lesions. The requirement for demonstration of superiority over placebo in a clinical endpoint bioequivalence study is not intended for establishing efficacy of the generic product. Equivalent efficacy and safety of a generic product is assumed if the product is bioequivalent to the RLD. Superior performance compared to placebo is needed to show that the study design is sufficiently sensitive to demonstrate a difference between products. Whereas neither the test nor reference product showed superiority over placebo for reduction in non-inflammatory lesions, the study cannot be considered sufficiently sensitive to show a difference between products for reduction in non-inflammatory lesions. Although such a difference might have been shown with enrollment of a study population with a higher baseline comedone count, in this case it is not reasonable to require the sponsor to conduct another study. The study demonstrated equivalent effectiveness for the endpoints (reduction in inflammatory lesions and global evaluation) upon which the RLD was approved and also demonstrated non-inferiority for the additional endpoint (reduction in non-inflammatory lesions) that was not considered in the determination of effectiveness for the RLD.

Recommendation

The bioequivalence study with clinical endpoints submitted in ANDA 65-112 demonstrates equivalent performance between the Atrix erythromycin benzoyl peroxide gel and the reference listed drug Benzamycin® for the endpoints (reduction in inflammatory lesions and global evaluation) upon which the RLD was approved and also demonstrates non-inferiority for reduction in non-inflammatory lesions, an additional endpoint in current acne vulgaris trials that was not considered important in the determination of effectiveness for the RLD. Therefore, this study is adequate to demonstrate bioequivalence between these two products.

Comments to be conveyed to the sponsor

1. We have completed our review of your request for dispute resolution dated November 4, 2003 and subsequent amendments dated December 2, 2003 and January 20, 2004, and have concluded that the bioequivalence study with clinical endpoints submitted to ANDA 65-112 on November 30, 2001 is adequate to demonstrate bioequivalence of your Erythromycin-Benzoyl Peroxide Topical Gel USP, 3%/5% to the reference listed drug Benzamycin® (Dermik Laboratories, Inc.).
2. Our decision is based on the fact that the primary endpoints specified in your protocol are those upon which the approval of the reference product was based. Your study

demonstrated equivalent performance of your product and the RLD for those endpoints and also demonstrated non-inferiority for percent reduction in non-inflammatory lesions, the additional endpoint currently used in the evaluation of acne vulgaris products.

3. Your study did not demonstrate superiority over placebo for the Investigator's Global Assessment when analyzed as a dichotomous endpoint as recommended by the Division of Dermatologic and Dental Products (DDDDP), using a score of 0 at the end of treatment as the definition of success. However, DDDDP agrees that the more subjective Investigator's Global Assessment can be removed from the bioequivalence studies for topical acne vulgaris products.

Dena R. Hixon MD 2/25/04

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

3/4/04

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:65-112 APPLICANT:Atrix Laboratories, Inc.

DRUG PRODUCT: Erythromycin-Benzoyl Peroxide Topical Gel, USP 3%, 5%

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

The data submitted to ANDA 65-112 are adequate to demonstrate bioequivalence of Atrix Laboratories, Inc.'s Erythromycin-Benzoyl Peroxide Topical Gel USP, 3%, 5%, with the reference listed drug, Benzamycin® Topical Gel, using the primary endpoint of percent reduction from baseline in inflammatory lesion count at week 12.

1. The primary endpoints specified in your protocol are those upon which the approval of the reference product was based. Your study demonstrated equivalent performance of your product and the RLD for those endpoints and also demonstrated non-inferiority for percent reduction in non-inflammatory lesions, the additional endpoint currently used in the evaluation of acne vulgaris products.

2. Your study did not demonstrate superiority over placebo for either the test or reference product with regard to the Investigator's Global Assessment when analyzed as a dichotomous endpoint as recommended by the Division of Dermatologic and Dental Products (DDDDP), using a score of 0 at the end of treatment as the definition of success. However, DDDDP agrees that the more subjective Investigator's Global Assessment can be removed from the bioequivalence evaluation of topical acne vulgaris products.

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

CC: ANDA 65-112
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HGD-600/ D. Hixon

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Endorsements: (Final with Dates)
HFD-600/D. Hixon DRH 3/4/04
HFD-650/D. Conner 3/4/04

BIOEQUIVALENCY - ACCEPTABLE

submission date:
~~November 30, 2001~~
~~April 29, 2002~~
~~November 4, 2003~~
February 23, 2004

Strengths: 3%, 5%
Outcome: UC

1. Study Amendment (STA) : February 23, 2004

Strengths: 3%, 5%
Outcome: UC

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

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 65-112 SPONSOR : Atrix Laboratories

DRUG AND DOSAGE FORM : Erythromycin and Benzoyl Peroxide Topical Gel USP

STRENGTH(S) : 3%/5%

TYPES OF STUDIES : Clinical endpoint

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic ___ New facility _____ For cause ____ Other ____	Inspection requested: (date) Inspection completed: (date)	

ASSOCIATE DIRECTOR FOR MEDICAL AFFAIRS, OGD : DENA R. HIXON, M.D.

INITIAL : DRH DATE : 3/10/04

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm.D.

INITIAL : DPC DATE : 3/8/04

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-112

STATISTICAL REVIEW(S)

Statistical Review

ANDA 65-112
Drug Product: Erythromycin-Benzoyl Peroxide Gel USP 3%, 5%
Sponsor: Atrix Laboratories, Inc.
Reference Listed Drug (RLD): Benzamycin® Topical Gel, Dermik Laboratories, Inc.
Submission Date: 12/31/2001

Reviewer: **Huaixiang Li, Ph.D., QMRS/OB/CDER**
Requestor: **Dena Hixon, MD, Carol Kim, Pharm.D., OGD/CDER, 9/5/02**
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Remark: The data sets (effitt, effeval, efficacy, exclude2, status, aer, and complete) used in this analysis were supplied by the firm on CD-ROM and received on May 15, 2002 by OGD.

Objectives of the study

This study was a double-blind, randomized, three treatment, parallel-group, vehicle-controlled study in 352 subjects with mild to severe acne vulgaris but otherwise healthy. The purpose of the study was to show the therapeutic equivalence between the test product, Atrix Laboratories, Inc., Erythromycin-Benzoyl Peroxide Topical Gel USP 3%, 5%, and the reference product, Dermik Laboratories, Inc., Benzamycin® Topical Gel and show effectiveness between the active treatments and placebo, gel vehicle.

Study Design

The study was a 3 arm parallel double-blind study in subjects with mild to severe acne vulgaris. The three gels were the test product, Atrix's Erythromycin-Benzoyl Peroxide gel, the reference product, Dermik's Benzamycin® gel and the placebo, a gel vehicle. A total of 352 males and females with age ranging from 12 to 54 were enrolled into the study and randomized to one of the three treatments. One hundred and forty (140) subjects were randomized to treatment with Atrix's Erythromycin-Benzoyl Peroxide gel, 142 to Dermik's Benzamycin® gel, and 70 to placebo. All treatments were applied to the full face once daily for 84 days (12 weeks). The subjects were examined at week 0 (pre-treatment), and at weeks 2, 4, 6, 8, and 12. A global acne assessment (0-8, 0=clear skin, 8=full facial involvement) and three lesion counts were assigned at each visit.

Outcome Variables

According to the protocol, the primary endpoints were percent reduction[1] from baseline for the global acne assessment score and inflammatory lesion count at week 12. The secondary endpoints were percent reduction for the non-inflammatory and total lesion

[1] The percent reduction/change from baseline is defined as baseline value minus the value at the visit and divided by the baseline value, then multiplied by 100.

count (sum of inflammatory and non-inflammatory lesion counts), the actual score and reduction from baseline for the global acne assessment score, inflammatory lesion count, non-inflammatory lesion count, and total lesion count at week 12.

Statistical Analysis Methods[2]

Efficacy Analysis

The comparisons for the global acne assessment and lesion counts were made between treatment arms at the (two-sided) 5% level of significance. The efficacy analysis for each active treatment was tested separately by comparing with the placebo. The arms should be similar at baseline (week 0), and the active treatment should be more distinguishable from placebo as the study progresses.

The efficacy analyses for percent change/reduction from baseline, actual score/count, reduction from baseline for the global acne assessment, inflammatory lesion count, non-inflammatory lesion count, and total lesion count were conducted by using a general linear model containing the variables, treatment and center. The means (least square means) and p-values were obtained from the general linear model. Two pairwise comparisons, test vs. placebo and reference vs. placebo, were done by including two treatments (test and placebo or reference and placebo) in each analysis.

In our review, the global acne assessments between treatments were also analyzed by using a proportional odds ratio model including the variable treatment. Two pairwise comparisons, test vs. placebo and reference vs. placebo, were done by including two treatments (test and placebo or reference and placebo) in each analysis.

Equivalence analysis

The compound hypothesis to be tested is:

H_0: $\mu_T/\mu_R \leq \theta_1$ or $\mu_T/\mu_R \geq \theta_2$

versus

H_A: $\theta_1 < \mu_T/\mu_R < \theta_2$

In accordance with the standard in OGD for equivalence analyses for continuous endpoints, α=0.05, θ_1=0.80, and θ_2=1.25. Consequently, for "Raw" (i.e. untransformed) endpoints the 90% confidence interval (corresponding to two 1-sided tests at level α=0.05, as described by Sasabuchi) based on Fieller's method is calculated for the equivalence test. The null hypothesis H_0 is rejected if the 90% confidence interval for μ_T/μ_R is contained in the (0.80, 1.25) interval. Rejection of the null hypothesis H_0 supports the conclusion of equivalence of the two products. Calculation of the 90% confidence intervals, using Fieller's method, was facilitated by using the GLM procedure

[2] There was no significant treatment by center interaction for raw, rank, and proportional odds ratio analyses for both efficacy and equivalence analyses except one case. For the efficacy analysis, P=0.039 for rank of percent improvement for total lesion count for ITT population at week 8.

in SAS®, including the variables treatment and center in the model. This resulted in putting equal weight on each center.

Rank Transformation analyses: We found that the percent change from baseline, actual count, and reduction from baseline for the global acne assessment score and three lesion counts, were strongly enough skewed that the assumption of normality of distribution was likely not the most appropriate for these data. We conducted the efficacy and equivalence analyses based on the rank value. The results were obtained from rank assignment by using the SAS® RANK procedure and the general linear model, containing the variables, treatment and center, by using the SAS® GLM procedure. This resulted in putting equal weight on each center. However, due to limited measurement levels for the global acne assessment (0-8), the percent change from baseline, the actual score, and reduction from baseline only had a small number of possible values. It is not suitable to do the equivalence test based on the rank value for the global acne assessment.

Proportional Odds Ratio analyses: The global acne assessment endpoints were also compared between the test and reference treatment groups by using the proportional odds ratio model containing the variable treatment (only the test and reference groups in the model). The estimated log odds ratio and 90% confidence interval were calculated and transferred back (using anti-logs) to the original scale. There is currently no established standard in OGD for setting equivalence limits when using the proportional odds method with ordered categorical endpoints. We used an approach analogous to the usual approach for binary endpoints as follows. Based on the traditional method used in OGD for binary outcomes, the absolute difference in proportions between the test and reference populations should be less than 0.2 in order to establish equivalence. When the reference proportion is 0.5, the range of the test proportions would be 0.3 to 0.7 for equivalence to be established. This is equivalent to the odds ratio ranging from 3/7 (0.429) to 7/3 (2.333). We used the limits (0.429, 2.333) to give an order of magnitude assessment of equivalence, acknowledging that this may be too stringent and has never been specified by OGD/OPS as the appropriate ones to use.

Analysis Populations

Two analysis populations were defined in the protocol and the sponsor's report:

Intent-to-treat population (ITT) – All subjects randomized to the treatment and treated with at least one dose of study medication.
Efficacy valid population (EFF) – All subjects in the ITT population who completed the study according to the protocol.

According to the FDA medical reviewers, the determination of clinical equivalence of the two active treatments was to be assessed using the efficacy-valid population (EFF), while the superiority comparison of the two active treatments to placebo was to be assessed using the intent-to-treat population (ITT).

Based on the SAS data sets submitted by the sponsor, the sponsor's intent-to-treat population (SITT) included 339 subjects randomized to treatment, and the sponsor's efficacy valid population (SEFF) was reduced to 265 subjects.

This table shows the three populations per treatment arm, as defined by the sponsor

Population	Erythromycin-Benzoyl Peroxide	Benzamycin®	Placebo	Total
Safety	140	142	70	352
Excluded from SITT	2	6	5	13
Baseline visit only	1	4	3	8
Noncompliance at week 12	1	2	1	4
Adverse event			1	1
SITT	138	136	65	339
Excluded from SEFF	31	27	16	74
Noncompliance	6	4	3	13
No clear acne diagnosis	1	2	0	3
Not evaluated by same examiner	18	16	8	42
Prohibited medication used	6	5	5	16
SEFF	107	109	49	265
Excluded/missed visit at week 12 from SEFF*	18	25	14	57
SEFF at week 12	89	84	35	208

*: There are four reasons for exclusion from the SEFF population: outside visit window (≥4 days), non-compliance, prohibited medication used, and adverse event. The subject could have one or more reasons out of these four reasons for being excluded from the SEFF population at the week 12 visit.

Modifications to the Sponsor's Analysis Populations

Based on the protocol, to be eligible, subjects should have ≥15 inflammatory lesions, ≥10 comedones, and ≤3 nodules at the baseline visit. However, four patients violated the requirement: Subjects #06086 (test), #06092 (reference), and #06186 (reference), had comedone counts of 9, 1, and 2, and yet were included in the SITT population. Subject #13155 (reference) had an inflammatory lesion count of 14 and yet was included in the SITT and SEFF populations. According to the FDA medical reviewer, these four subjects should be excluded from our ITT population and subject #13155 should be excluded from our EFF population for our statistical analyses.

Population	Erythromycin-Benzoyl Peroxide	Benzamycin®	Placebo	Total
ITT	137	133	65	335
EFF	107	108	49	264
EFF at week 12	89	83	35	207

Analysis Results

Demographics and baseline (Safety population)

There was no significant difference between treatment arms for any of the actual score/count variables at week 0 except inflammatory lesion count for the ITT population (p=0.036).

Age, sex, and race were comparably distributed among the three treatment groups for safety population as shown in the following table.

	Erythromycin-Benzoyl Peroxide	Benzamycin®	Placebo	Total
Age				
Mean	19.25	18.27	18.87	18.78
Median	16	16	16	16
Range	12 - 51	12 - 54	12 - 44	12 - 54
Sex				
Male	75	68	37	180
Female	65	74	33	172
Race				
White	101	97	54	252
Black	29	30	11	70
Hispanic	5	9	2	16
Asian	3	2	3	8
Other	2	4	0	6

Primary endpoints: Percent change from baseline at week 12 (raw and rank analyses)

Efficacy Analysis

A summary of the results from the general linear model for the global acne assessment and lesion counts for the ITT population at week 12 is given in Table 1.1 below.

Table 1.1: Efficacy analysis (percent change from baseline) – global acne assessment and lesion counts (raw and rank values) for the ITT population at week 12

	Test vs. placebo			Ref. vs. placebo		
Variable	Test Drug LS Mean	Placebo LS Mean	p-value	Ref. Drug LS Mean	Placebo LS Mean	p-value
Raw						
Global acne assessment	**41.33**	**30.01**	**0.020**	**46.77**	**30.64**	**<0.001**
Inflammatory lesion	**47.73**	**33.22**	**0.019**	**53.18**	**34.00**	**<0.001**
Non-inflammatory lesion	25.84	18.58	0.331	23.65	17.51	0.444
Total lesion	38.49	25.36	0.015	39.76	25.56	0.005
Rank						
Inflammatory lesion	**111.54**	**82.10**	**<0.001**	**111.94**	**78.86**	**<0.001**
Non-inflammatory lesion	108.15	92.56	0.066	105.03	89.44	0.069
Total lesion	111.24	85.17	0.002	109.15	83.23	0.002

The test and reference treatments were significantly better than placebo for the raw value analyses of the global acne assessment, and for both raw and rank value analyses of the inflammatory lesion count and total lesion count for the ITT population. However, the test and reference treatments were not significantly better than placebo for both raw and rank value analyses of the non-inflammatory lesion count for the ITT population ($p \geq 0.066$).

Equivalence Analysis

The confidence intervals for the percent change from baseline (raw and rank values) for the global acne assessment and lesion counts for the EFF population at week 12 are summarized in Tables 1.2.

Table 1.2: Equivalence Analysis (percent change from baseline) – global acne assessment and lesion counts (raw and rank values) for the EFF population at week 12

	Raw				Rank	
variable	Test LS mean	Ref. LS mean	90% Confidence Interval (%)	Pass/Fail	90% Confidence Interval (%)	Pass/Fail
Global acne assessment	**45.35**	**46.82**	**83.1, 112.9**	**P**		
Inflammatory lesion	**53.67**	**53.68**	**84.1, 119.0**	**P**	**93.4, 115.5**	**P**
Non-inflammatory lesion	24.92	20.40	67.6, 247.0	F	88, 153	F
Total lesion	41.16	39.02	85.9, 130.3	F	92, 128	F

The equivalence test passed for the raw value of the global acne assessment for the EFF population at week 12. The equivalence test passed for the inflammatory lesion count, but failed for the non-inflammatory lesion count and total lesion count for both raw and rank values for the EFF population at week 12.

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Secondary endpoints

Actual score/count and the reduction from baseline at week 12 (raw and rank values)

Table 2.1: Efficacy analysis (actual score/count and reduction from baseline) – global acne assessment and lesion counts for the ITT population at week 12

	Test vs. placebo			Ref. vs. placebo		
Variable	Test Drug LS Mean	Placebo LS Mean	p-value	Ref. Drug LS Mean	Placebo LS Mean	p-value
Actual score/count						
Raw Global acne assessment	2.46	2.94	0.028	2.30	2.92	0.003
Inflammatory lesion	17.91	19.19	0.5568	15.56	18.80	0.141
Non-inflammatory lesion	28.07	34.20	0.1618	28.79	34.46	0.166
Total lesion	45.98	53.38	0.1977	44.35	53.26	0.078
Rank Inflammatory lesion	99.02	107.51	0.329	91.45	112.50	0.012
Non-inflammatory lesion	95.99	108.46	0.110	95.84	104.04	0.303
Total lesion	96.78	109.63	0.119	94.45	106.83	0.133
Reduction from baseline						
Raw Global acne assessment	1.71	1.16	0.003	2.02	1.18	<0.001
Inflammatory lesion	18.51	11.43	0.014	18.74	11.82	0.010
Non-inflammatory lesion	8.77	7.88	0.784	12.45	7.66	0.182
Total lesion	27.28	19.31	0.110	31.18	19.49	0.016
Rank Inflammatory lesion	113.54	78.61	<0.001	112.72	76.21	<0.001
Non-inflammatory lesion	105.40	96.66	0.312	104.65	88.51	0.060
Total lesion	111.20	86.09	0.003	109.92	81.39	<0.001

Actual score/count: The test and reference treatments were not significantly better than placebo for all except three cases: p=0.028 for test versus placebo and p=0.003 for reference versus placebo for the global acne assessment score, and p=0.012 for reference versus placebo for the rank analysis of the inflammatory lesion count.

Reduction from baseline: The test and reference treatments were significantly better than placebo for the raw value of the global acne assessment, both raw and rank analyses of the inflammatory lesion count, and total lesion count rank analysis. The test treatment was not significantly better than placebo for the raw value of the total lesion count (p=0.110). The test and reference treatments were not significantly better than placebo for both raw and rank values of the non-inflammatory lesion count (p≥0.060).

Table 2.2: Equivalence Analysis (the actual score/count and the reduction from baseline) - (raw and rank analyses) for the EFF population at week 12

	Raw				Rank	
Variable	Test LS mean	Ref. LS mean	90% Confidence Interval (%)	Pass /Fail	90% Confidence Interval (%)	Pass /Fail
Actual score/count						
Global acne assessment	2.35	2.31	87.9, 118.1	P		
Inflammatory lesion	15.64	14.34	90.1, 132.8	F	81, 128	F
Non-inflammatory lesion	27.23	29.64	74.1, 113.6	F	65, 102	F
Total lesion	42.87	43.98	82.2, 115.7	P	75.7, 110	F
Reduction from baseline						
Global acne assessment	1.82	2.02	77.7, 105	F		
Inflammatory lesion	21.63	19.52	90.3, 137	F	81, 120	P
Non-inflammatory lesion	9.79	10.70	57.2, 145.3	F	58, 123	F
Total lesion	31.42	30.21	83, 131	F	75, 118	F

Actual score/count: For the EFF population at week 12 the equivalence test failed for all variables except two cases. The equivalence test passed for the raw value of the global acne assessment and for the rank analysis of total lesion count.

Reduction from baseline: The equivalence test failed for all variables for the EFF population at week 12 except the rank analysis of the inflammatory lesion count.

Global acne assessment at week 12 (actual score) – Proportional Odds Ratio analysis

The results using the proportional odds ratio model for the global acne assessment (actual score) at week 12 for the ITT and EFF populations are summarized in Table 2.3.

Table 2.3: Efficacy and equivalence analysis (global acne assessment) - odds ratio model*

	ITT – efficacy analysis				EFF- equivalence analysis			
	Test vs. placebo		Reference vs. placebo		Test vs. reference			
Week	Odds ratio	p-value	Odds ratio	p-value	Odds ratio	Lower limit	Upper limit	Within limits of (0.429, 2.333)
12	1.597	0.080	2.000	0.011	0.965	0.568	1.638	Yes

*: The odds ratios and p-values were obtained from the pairwise comparison of the proportional odds ratio model containing the variable treatment.

The reference treatment was significantly better than placebo (p=0.011), but not the test treatment (p=0.080) for the ITT population at week 12. The confidence interval, test versus reference, for the odds ratio for global acne assessment was contained in the (0.429, 2.333) interval for the EFF population at week 12.

Additional analyses – week 8

As requested by the FDA medical reviewer, additional analyses were performed for percent change from baseline, actual score/count, and reduction from baseline for the global acne assessment and three lesion counts at week 8. The reasons for exclusion/missed visit from EFF population at week 8 were the same as for week 12 (please see details in page 4).

Population	Erythromycin-Benzoyl Peroxide	Benzamycin®	Placebo	Total
EFF at week 8	89	87	31	207

Table 3.1: Efficacy analysis (percent change from baseline) – global acne assessment and lesion counts (raw and rank values) for the ITT population at week 8

	Test vs. placebo			Ref. vs. placebo		
Variable	Test Drug LS Mean	Placebo LS Mean	p-value	Ref. Drug LS Mean	Placebo LS Mean	p-value
Raw						
Global acne assessment	39.01	22.85	<0.001	38.33	23.01	<0.001
Inflammatory lesion	51.50	23.24	<0.001	48.36	23.15	<0.001
Non-inflammatory lesion	24.56	7.67	0.008	21.86	7.32	0.075
Total lesion	38.32	16.69	<0.001	37.46	16.71	<0.001
Rank						
Inflammatory lesion	118.76	69.27	<0.001	114.27	71.56	<0.001
Non-inflammatory lesion	110.19	83.59	0.002	108.25	81.27	0.002
Total lesion	115.75	74.51	<0.001	112.54	74.36	<0.001

The test and reference treatments were significantly better than placebo for both raw and rank values of all variables except the reference versus placebo for the raw value of the non-inflammatory lesion count.

Table 3.2: Equivalence Analysis (percent change from baseline) – global acne assessment and lesion counts (raw and rank values) for the EFF population at week 8

	Raw				**Rank**	
variable	Test LS mean	Ref. LS mean	90% Confidence Interval (%)	Pass /Fail	90% Confidence Interval (%)	Pass /Fail
Global acne assessment	41.09	39.85	87.7, 121.4	P		
Inflammatory lesion	53.28	47.28	95.2, 134.1	F	93.5, 123	P
Non-inflammatory lesion	27.00	18.53	79.9, 336.0	F	75, 137	F
Total lesion	40.90	36.76	91.7, 135.9	F	92, 131	F

The equivalence test passed for the global acne assessment score and for the rank value of the inflammatory lesion count, but failed for all other variables.

Table 3.3: Efficacy analysis (actual score and reduction from baseline) – global acne assessment and lesion counts for the ITT population at week 8

	Test vs. placebo			Ref. vs. placebo		
Variable	Test Drug LS Mean	Placebo LS Mean	p-value	Ref. Drug LS Mean	Placebo LS Mean	p-value
Actual score/count						
Raw						
Global acne assessment	2.55	3.23	<0.001	2.65	3.23	0.002
Inflammatory lesion	17.08	22.36	0.010	16.32	22.20	0.003
Non-inflammatory lesion	29.38	39.24	0.048	29.52	39.32	0.032
Total lesion	46.46	61.60	0.014	45.84	61.53	0.004
Rank						
Inflammatory lesion	92.91	118.91	0.003	89.20	119.36	<0.001
Non-inflammatory lesion	95.00	113.23	0.017	94.75	107.18	0.116
Total lesion	94.47	116.04	0.010	92.10	112.87	0.010
Reduction from baseline						
Raw						
Global acne assessment	1.61	0.86	<0.001	1.67	0.87	<0.001
Inflammatory lesion	19.35	8.26	<0.001	17.98	8.43	<0.001
Non-inflammatory lesion	7.45	2.84	0.158	11.71	2.80	0.010
Total lesion	26.80	11.10	<0.001	29.69	11.22	<0.001
Rank						
Inflammatory lesion	118.64	69.04	<0.001	114.15	72.02	<0.001
Non-inflammatory lesion	108.39	85.79	0.010	108.48	80.10	0.001
Total lesion	116.10	73.33	<0.001	113.88	70.85	<0.001

Actual score/count: The test and reference treatments were significantly better than placebo for all variables except the reference versus placebo for the rank value of the non-inflammatory lesion count.

Reduction from baseline: The test and reference treatments were significantly better than placebo for all variables except the test versus placebo for the actual (raw) value of the non-inflammatory lesion count.

Table 3.4: Equivalence Analysis (actual score and reduction from baseline) - (raw and rank values) for the EFF population at week 8

	Raw				Rank	
variable	Test LS mean	Ref. LS mean	90% Confidence Interval (%)	Pass /Fail	90% Confidence Interval (%)	Pass /Fail
Actual score/count						
Global acne assessment	2.51	2.54	87, 112.1	P		
Inflammatory lesion	17.14	16.90	82.8, 124.6	P	82, 123	P
Non-inflammatory lesion	28.08	28.60	80, 120.6	P	73, 111	F
Total lesion	45.22	45.49	84.2, 117.5	P	81, 116	P
Reduction from baseline						
Global acne assessment	1.69	1.72	83.1, 115.5	P		
Inflammatory lesion	21.21	19.29	87.1, 140	F	92, 144	F
Non-inflammatory lesion	9.93	11.30	58.2, 130.7	F	58, 125	F
Total lesion	31.14	30.59	81.5, 127.6	F	82.7, 127.8	F

Actual score/count: The equivalence test passed for all variables except one case. The equivalence test failed for the rank values of the non-inflammatory lesion count.

Reduction from baseline: The equivalence test failed for all variables except the raw value of the global acne assessment score.

Table 3.5: Efficacy and equivalence analysis (global acne assessment) at week 8 - odds ratio model

	ITT – efficacy analysis				EFF- equivalence analysis			
	Test vs. placebo		Reference vs. placebo		Test vs. reference			
Week	Odds ratio	p-value	Odds ratio	p-value	Odds ratio	Lower limit	Upper limit	Within limits of (0.429, 2.333
8	2.191	0.004	2.167	0.005	1.004	0.593	1.700	Yes

The test and reference treatments were significantly better than placebo ($p \leq 0.005$). The confidence interval, test versus reference, for the odds ratio was contained in the (0.429, 2.333) interval.

Safety

A total of 262 adverse events were reported during the study for 122 subjects: 52 subjects (128 events) in the test group, 47 subjects (96 events) in the reference group, and 23 subjects (38 events) in the placebo group. The events included headache, cold symptoms, facial dryness/erythema, sore throat, sinus congestion, etc. Forty-eight events out of 262 events were considered possibly or probably related to the study therapy, but were not severe.

There were 15 severe events reported by 9 subjects: 4 subjects (9 events) in the test group and 5 subjects (6 events) in the reference group, of the total of 262 events. These were not considered related to the treatments.

No statistically significant differences were found between test and reference groups for the adverse events during the study.

Comments on the Sponsor's Analyses

The sponsor performed efficacy analysis for the sponsor's intent-to-treat (SITT) population and equivalence test for the sponsor's efficacy-evaluable (SEFF) population for global acne assessment, inflammatory lesion count, non-inflammatory lesion count and total lesion at week 12. The sponsor used a general linear model including the variables treatment and center.

Percent change from baseline at week 12: the reference treatment was significantly better than placebo for global acne assessment, inflammatory lesion count, and total lesion count, but not for non-inflammatory lesion count, for the SITT population. The equivalence test passed for global acne assessment and inflammatory lesion count, but failed for non-inflammatory lesion count and total lesion count for the SEFF population. Their results were summarized in the FDA medical report and were similar to those in this report.

The sponsor also provided the results for actual score and reduction from baseline for global acne assessment, inflammatory lesion count, non-inflammatory lesion count and total lesion count for both populations at week 12. There were some discrepancies between our results and the sponsor's. However, the differences were not important.

Summary

Efficacy: The table below summarizes the non-significant results ($p > 0.05$) from the efficacy analyses for the ITT population at weeks 12 and 8.

	Percent change from baseline*		Actual score /count*		Reduc-tion from baseline *	
	Raw	Rank	Raw	Rank	Raw	Rank
Week 12						
Global acne assessment			#			
Inflammatory lesion			(T_P) (R_P)	(T_P)		
Non-inflammatory lesion	(T_P) (R_P)	(T_P) (R_P)	(T_P) (R_P)	(T_P) (R_P)	(T_P) (R_P)	(T_P) (R_P)
Total lesion			(T_P) (R_P)	(T_P) (R_P)	(T_P)	
Week 8						
Global acne assessment						
Inflammatory lesion						
Non-inflammatory lesion	(R_P)			(R_P)	(T_P)	
Total lesion						

*: T_P = Test vs. Placebo, R_P = Reference vs. Placebo.
#: p = 0.080 for test versus placebo from odds ratio model.

At week 12: The global acne assessment score had one non-significant difference, test versus placebo, from the odds ratio model analysis applied to actual scores. The test and reference treatments were not significantly better than placebo for both raw and rank values of all three measurements for the non-inflammatory lesion count. The test and reference treatments were not significantly better than placebo for both raw and rank values of the actual count for the inflammatory lesion count and total lesion count except one case. The test was not significantly better than placebo for the raw value of reduction from baseline for the total lesion count.

At week 8: There were three non-significant differences for the non-inflammatory lesion count: reference versus placebo for the raw value of percent change from baseline and for the rank value of actual count, and test versus placebo for the raw value of reduction from baseline.

Equivalence: The table below summarized the results from the equivalence testing between test and reference treatments for the EFF population at week 8 and 12.

	Percent change from baseline		Actual score /count		Reduction from baseline	
	Raw	Rank	Raw	Rank	Raw	Rank
Week 12						
Global acne assessment	**P**		**P#**		F	
Inflammatory lesion	**P**	**P**	F	F	F	**P**
Non-inflammatory lesion	F	F	F	F	F	F
Total lesion	F	F	**P**	F	F	F
Week 8						
Global acne assessment	**P**		**P#**		**P**	
Inflammatory lesion	F	**P**	**P**	**P**	F	F
Non-inflammatory lesion	F	F	**P**	F	F	F
Total lesion	F	F	**P**	**P**	F	F

#: The confidence intervals, test versus reference, for the odds ratio for global acne assessment were contained in the (0.429, 2.333) interval for the EFF population at week 8 and 12.

At week 12: The global acne assessment score had one failure, the raw value of reduction from baseline, for the equivalence testing. For the Inflammatory Lesion Count the equivalence test passed for both raw and rank values of percent change from baseline and the rank value of reduction from baseline, but failed for both raw and rank values of actual count and the raw value of reduction from baseline. For the Non-inflammatory Lesion Count and the Total Lesion Count the equivalence test failed for both raw and rank values of all three measurements, except one case (the raw value of actual count for the total lesion count).

At week 8: The equivalence test passed for all three measurements for the global acne assessment. For Inflammatory Lesion Count the equivalence test passed for the rank value of percent change from baseline and for the raw and rank values of actual count, but failed the raw value of percent change from baseline and the raw and rank values of reduction from baseline. The non-inflammatory lesion count only passed the equivalence

test for the raw value of actual count and the total lesion count passed for raw and rank values of actual count.

Conclusion

In terms of the stated primary endpoints – percent change from baseline for the global acne assessment score and the inflammatory lesion count at week 12 – both the test and reference products were statistically significantly better than placebo in the study, and test and reference were shown to be equivalent. This finding is supported by results at week 8, where test and reference were also shown to be superior to placebo, test and reference were shown to be equivalent for the global acne assessment score, and test and reference passed the equivalence test using the rank transformation analysis for inflammatory lesion count.

In terms of the other percent change from baseline endpoints – non-inflammatory lesion count and total lesion count - the test and reference treatments were not significantly better than placebo for non-inflammatory lesion count at week 12, and equivalence has not been shown for the non-inflammatory lesion count and total lesion count at week 12. At week 8, the test and reference treatments were statistically significantly better than placebo for non-inflammatory lesion count based on the rank transformation analysis, and the test treatment was statistically significantly better than placebo for non-inflammatory lesion count analyzing the raw values. However, equivalence has not been shown for the non-inflammatory lesion count and total lesion count at week 8.

Results for endpoints based on actual scores/counts and on change from baseline (as opposed to *percent* change) have been summarized above. We note that actual counts at week 8 represent the only case where equivalence was shown for non-inflammatory lesions.

Huaixiang Li 7/18/03

Huaixiang Li, Ph.D.
Mathematical Statistician, QMR

Donald J. Schuirmann 7/18/03

Donald J. Schuirmann
Expert Mathematical Statistician, QMR

Stella G. Machado 7/18/03

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

cc:
HFD-655 Dena R. Hixon, Carol Y. Kim, Krista Scardina
HFD-705 Stella G. Machado, Donald J. Schuirmann, Huaixiang Li
HFD-705 QMR Chron

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-112

ADMINISTRATIVE DOCUMENTS

M E M O R A N D U M

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

DATE : December 17, 2001

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615)

12/17/2001

SUBJECT: Examination of the Clinical bioequivalence study submitted with an ANDA for Erythromycin and Benzoyl Peroxide Topical Gel USP, 3%; 5%to determine if the application is substantially complete for filing.

Atrix Laboratories, Inc. has submitted ANDA 65-112 for Erythromycin and Benzoyl Peroxide Topical Gel USP, 3%;5%. The ANDA contains a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the Clinical bioequivalence study is complete, and could establish that the product is bioequivalent.

Please evaluate whether the request for study submitted by Atrix on November 30, 2001 for its Erythromycin and Benzoyl Peroxide product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

In determining whether a bio study is "complete" to satisfy statutory requirements, the following items are examined:

1. Study design

   (a) Appropriate number of subjects
   (b) Description of methodology

2. Study results

   (a) Individual and mean data is provided
   (b) Individual demographic data
   © Clinical summary

The issue raised in the current situation revolves around whether the study can purport to demonstrate bioequivalence to the listed drug.

We would appreciate a cursory review and your answers to the above questions as soon as possible so we may take action on this application.

DIVISION OF BIOEQUIVALENCE:

1/16/02

X Study meets statutory requirements

~~X~~ Study does **NOT** meet statutory requirements

Reason:

ACCEPT FOR FILING

1/16/2002

(SEE LAST PAGE).

_____ Waiver meets statutory requirements

_____ Waiver does **NOT** meet statutory requirements

Reason: Composition of the test product is not Q1 & Q2 Same as that of the RLD (NDA 50557). A safety study may be required for the acceptance of such topical products. Dr. Fanning should be consulted to determine the requirements of a safety study.

Director, Division of Bioequivalence — 1/16/02 Date

BIOEQUIVALENCE CHECKLIST FOR APPLICATION COMPLETENESS

ANDA DRUG NAME FIRM

DOSAGE FORM(s)

	YES	NO	REQUIRED AMOUNT	AMOUNT SENT	COMMENTS
Protocol	✓				Appendix 1.1
Assay Methodology	N/A				Clinical End point study.
Procedure SOP	✓				
Methods Validation	N/A				Clinical Study
Study Results Ln/Lin	✓				
Adverse Events	✓				
IRB Approval	✓				
Dissolution Data	N/A				
Pre-screening of patients	✓				
Chromatograms	N/A				
Consent forms	✓				
Composition	✓				See Reviewer's Comments
Summary of study	✓				
Individual Data & Graphs , Linear & Ln	N/A				
PK/PD data disk		X			
Randomization Schedule	✓	✓			
Protocol Deviations	✓				

	YES	NO	REQUIRED AMOUNT	AMOUNT SENT	COMMENTS
Clinical site	✓				
Analytical site	N/A				
Study investigators	✓				
Medical Records	✓				
Clinical Raw Data	✓				
Test Article Inventory	✓				
BIO Batch Size	✓	✓			[redacted]
Assay of active content drug	✓				
Content uniformity	✓				
Date of manufacture	✓				
Exp. Date RLD					
Biostudy lot numbers	✓				
Statistics	✓				
Summary results provided by the firm indicate studies pass BE criteria	✓				
Waiver requests for other strengths / supporting data	NA				

Additional comments:

1/16/02

Recommendation: COMPLETE / INCOMPLETE Composition of the test product is not Q1 and Q2 same as the RLD (NDA 50557). Therefore, a safety study may be required to support product approval. Dr. Fanning should be consulted to determine if a safety study is required

Reviewed by
Gurpal Sijh 12-18-01

Date _____

Revised 6/7/2000

1/16/2002 10:10 AM.

I CONSULTED DR. FANNING ABOUT THE SAFETY ISSUE.
SHE SAID - 1. IN THE CLINICAL STUDY
THE ADVERSE EVENT ARE EVALUATED
THUS, A SAFETY IS ALSO CHECKED WITH
EFFICACY.

2. NO SEPARATE SAFETY STUDY IS NECESSARY.
3. THE INACTIVE INGREDIENTS ARE COMMON
AND THEREFORE DO NOT RAISE ANY SAFETY
CONCERN.

THEREFORE ANDA SHOULD BE ACCEPTED FOR FILING.

(S. G. NERURKAR)
TEAM LEADER BR2

RECORD OF TELEPHONE CONVERSATION

On September 27, 2002, we contacted Atrix Laboratories, Inc. (Atrix) and made reference to their ANDA 65-112.

We requested the following from Atrix:

1. Please include the test and release specification for the limit of ———— in the drug substance Erythromycin as per USP 25.

2. Since the drug product is used for delayed use (DU) for three months, please show that your ———— procedure for erythromycin in the drug product is stability-indicating.

Ms. Coressel informed us that she will discuss the two requests with the chemist and either call us back with questions or submit their response as a telephone amendment.

On September 30, 2002, we contacted Atrix in response to their request for a follow-up teleconference.

Atrix requested to discuss the second request.

We clarified that the Agency wants to know if Erythromycin ————————————————————

Atrix representatives informed us that Atrix is following the ————————————————————

We instructed Atrix to submit their explanation in the telephone response.

Atrix representatives agreed to do so.

DATE:
9/27/02 & 9/30/02

ANDA NUMBER
65-112

TELECON INITIATED BY AGENT

PRODUCT NAME:
Erythromycin and Benzoyl Peroxide Topical Gel USP, 3%;5%

FIRM NAME:
Atrix Laboratories, Inc.

FIRM REPRESENTATIVES:
1. Kathy Coressel
2. Chris French, Director of Dermatologic
3. David Osborne, VP of Derm Division
4. Mark Sweeney, VP of QA
5. Jim Menro, Lead Chemist
6. Kim Itzen, Stability Coordinator
7. Jill Laden, Superviosr of QC

TELEPHONE NUMBER:
970-482-5868 ext. 251

FDA REPRESENTATIVES
Gil Kang
James Fan
Sarah Ho

SIGNATURES:
G.Kang GK 10/4/02
J.Fan 10/4/02
S.Ho 10/4/02

Orig: ANDA 65-112
Cc: Division File
Chem. I Telecon Binder
V:\FIRMSAM\ATRIX\Telecon\65112.27sep2002.doc

RECORD OF TELEPHONE CONVERSATION

On this date, we contacted Atrix Laboratories, Inc. (Atrix) and made reference to their ANDA 65-112 and to our previous teleconferences on September 27, and September 30, 2002.

We informed Atrix representatives that after discussion with upper management regarding the second deficiency in our previous teleconferences, it was recommended that Atrix

[redacted]

product.

The firm asked whether this is method is for release or stability or both.

We clarified that it is generally for delayed release for stability, both requested for the firm to submit data for both.

[redacted]

Atrix representatives agreed to submit the above information as a telephone amendment.

DATE:
10/7/02

ANDA NUMBER
65-112

TELECON INITIATED BY AGENT

PRODUCT NAME:
Erythromycin and Benzoyl Peroxide Topical Gel USP, 3%;5%

FIRM NAME:
Atrix Laboratories, Inc.

FIRM REPRESENTATIVES:
1. Kathy Coressel
2. Chris French, Director of Dermatologic
3. David Osborne, VP of Derm Division
4. Mark Sweeney, VP of QA
5. Jim Menro, Lead Chemist
6. Kim Itzen, Stability Coordinator
7. Jill Laden, Superviosr of QC

TELEPHONE NUMBER:
970-482-5868 ext. 251

FDA REPRESENTATIVES
Gil Kang
James Fan
Sarah Ho

SIGNATURES:
G.Kang GK 11/7/02
J.Fan 11/13/02
S.Ho

Orig: ANDA 65-112
Cc: Division File
Chem. I Telecon Binder
V:\FIRMSAM\ATRIX\Telecon\65112.7oct2002.doc

RECORD OF TELEPHONE CONVERSATION

I telephoned Atrix Laboratories and requested a commitment to change the storage temperature recommendation on the insert labeling, under prior to reconstitution to:
Store at 20-25°C (68-77°F)[see USP Controlled Room Temperature]

The firm will provide a commitment to change the storage temperature as stated above at the time of next printing.

DATE
March 1, 2004

ANDA NUMBER
65-112

IND NUMBER

TELECON

INITIATED BY

SPONSOR X

FDA

PRODUCT NAME
Erythromycin and Benzoyl Peroxide Topical Gel, USP

FIRM NAME
Atrix Laboratories

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Lynn Hansen
Cody Yarborough

TELEPHONE NUMBER
370 482-5868

SIGNATURE
Michelle Dellabella

V:\FIRMSAM\ATRIX\Telecon\65112tcon3012004.doc

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 65-112

CORRESPONDENCE

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

ATRIX
LABORATORIES, INC.

PHONE: (970) 482-5868
FAX: (970) 482-9735
EMAIL: atrixlab@frii.com
http://www.atrixlabs.com

1/14/02
Ack for filing
505(j)(2)(A)
S. Middleton

VIA FEDERAL EXPRESS

ORIGINAL ANDA

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

Concur.
15-JAN-2002
Gregory B. Davis 65-112

November 30, 2001

**RE: Erythromycin and Benzoyl Peroxide Topical Gel USP, 3%;5%
Original Abbreviated New Drug Application**

Dear Mr. Buehler:

Atrix Laboratories, Inc. is hereby submitting an Abbreviated New Drug Application for Erythromycin and Benzoyl Peroxide Topical Gel USP, 3%;5% as required by Section 505 (j) of the Federal Food, Drug, and Cosmetic Act, and in accordance with 21 CFR Part 314.92 and 314.94.

Pursuant to 21 CFR 314.94(a)(2), each volume contains a comprehensive table of contents indicating the page number(s) of the submission's contents. The blue archival and red chemisty copies (**8** volumes each) contain the complete application. The orange bioavalability/bioeqivalence section review copy (5 volumes) contains the bioequivalence information.

The Methods Validation package is provided in a brown binder and contains duplicate copies of the raw material and finished product specifications, methods, and analytical results. Atrix Laboratories commits to resolve any issues identified in the methods validation process post-approval.

This information is submitted for your review and approval. Please acknowledge receipt of this submission by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

Atrix Laboratories, Inc.

Chris L. French
Chris L. French
Director, Dermatology Business Unit
Enclosures

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
DEC 03 2001
OGD

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information from

ATRIX LETTER OF 11/30/01

Atrix Laboratories, Inc.
Erythromycin and Benzoyl Peroxide Topical Gel USP, 3%;5%

Erythromycin Benzoyl Peroxide Topical Gel, USP 3%, 5% is clinically bioequivalent to Benzamycin®.

This ANDA is contained in 8 volumes and organized in the manner recommended by the Office of Generic Drugs "*Guidance for Industry, Organization of an ANDA, February 1999*". The recommended 21 sections, each of which is designated by a Roman numeral, are represented. A table of contents is provided which cross-references each section, along with significant parts of the individual section, to the actual page number where the section or part begins. Tables of contents for individual sections containing attachments are also provided. The major sections of the application are identified with white tabs and Roman numerals. The sub-sections are identified with blue tabs and the designated number. Each technical section is prefaced with a short summary to highlight technical information.

For ease of reference, the entire application is numbered sequentially in the bottom center such that both text and attachments bear consecutive numbering.

Atrix is filing an archival copy (in blue folder) of the ANDA, a technical review copy (in red and orange folders), and a field copy sent to the Colorado District Office (in burgundy folders). The technical review copy and the field copies are identical to the archival copy, and a certification attesting to this is provided with the field copy. Four copies of the draft labeling are included in all copies of this ANDA.

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

ATRIX
LABORATORIES, INC.

PHONE: (970) 482-5868
FAX: (970) 482-9735
EMAIL: atrixlab@frii.com
http://www.atrixlabs.com

VIA FEDERAL EXPRESS

FAX AMENDMENT

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

NEW CORRESP

1/10/02

RE: ANDA # 65-112 Erythromycin and Benzoyl Peroxide Topical Gel USP, 3%;5%
FAX Amendment- CMC

Dear Mr. Buehler:

Atrix Laboratories, Inc. is hereby submitting an amendment to our unapproved Abbreviated New Drug Application for Erythromycin and Benzoyl Peroxide Topical Gel USP, 3%;5% as required by Section 505 (j) of the Federal Food, Drug, and Cosmetic Act, and in accordance with 21 CFR Part 314.96.

Reference is made to a phone conversation on January 9, 2002 between Sandra Middleton of FDA and Chris French of Atrix.

Information pertaining to the reconciliation of the batches was provided on pages 636-637 of the original application, however we are providing a summary, in a table format, and clarification as requested for ease of review.

This information is submitted for your review and approval. Please acknowledge receipt of this submission by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

Atrix Laboratories, Inc.

Chris L. French
Director, Dermatology Business Unit
Enclosures

ANDA 65-112

JAN 16 2002

Atrix Laboratories, Inc.
Attention: Chris L. French
2579 Midpoint Drive
Fort Collins, CO 80525-4417

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 the telephone conversation dated January 9, 2002 and your correspondence dated January 11, 2002.

NAME OF DRUG: Erythromycin and Benzoyl Peroxide Topical Gel USP, 3%;5%

DATE OF APPLICATION: November 30, 2001

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 3, 2001

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:

Mark Anderson
Project Manager
(301) 827-5849

Sincerely yours,

Gregory S. Davis for

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

ANDA 65-112
cc: DUP/Jacket
Division File
Field Copy
HFD-610/R.West
HFD-610/P.Rickman
HFD-92
HFD-615/M.Bennett
HFD-600/
Endorsement:
HFD-615/GDavis, Chief, RSB GDavis 16-JAN-2002 date
HFD-615/SMiddleton, CSO S. Middleton date 1/14/02
Word File
V:\FIRMSAM\ATRIX\LTRS&REV\65112.ACK
F/T EEH 01/14/02
ANDA Acknowledgment Letter!

MINOR AMENDMENT

ANDA 65-112

MAR 14 2002

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Atrix Laboratories, Inc. TEL: 970-482-5868 ext. 373

ATTN: Chris L. French FAX: 970-482-9735

FROM: Sarah Ho PROJECT MANAGER: 301-827-5754

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated November 30, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Erythromycin and Benzoyl Peroxide Topical Gel USP, 3%;5%.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (4 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:
CMC comments provided. Please include in your response.

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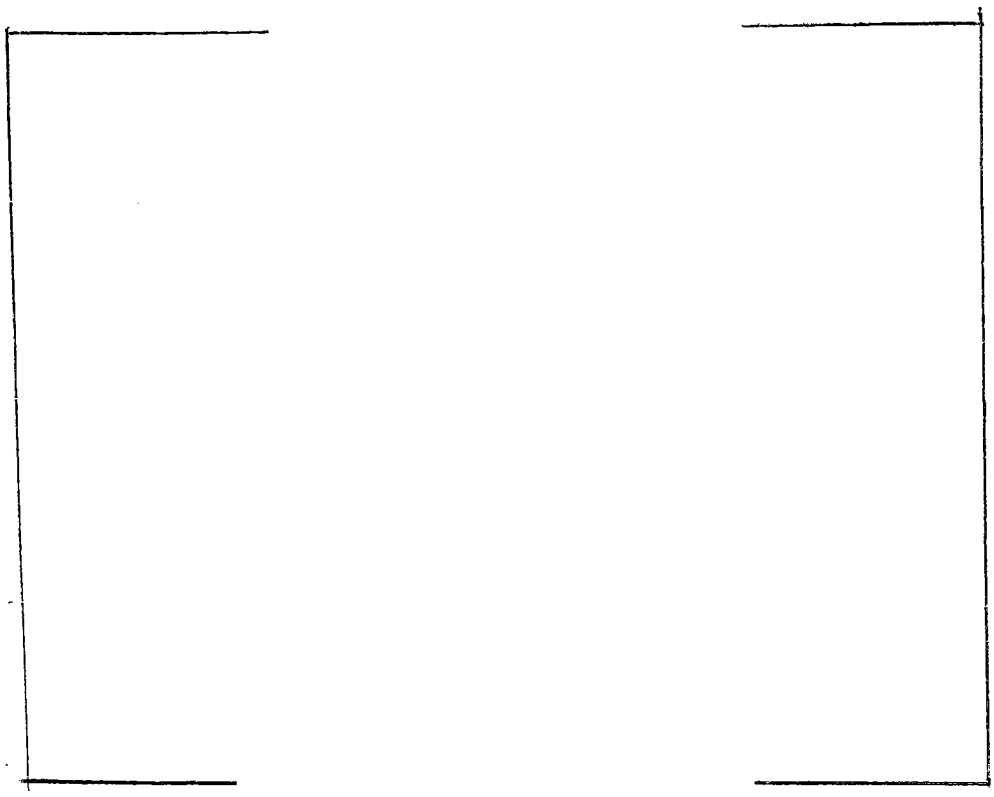
3/14/2002 FDA FAX

14.

15.

16.

17.



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

1. Please submit all available long-term stability data.

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

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

4. All facilities referenced in the ANDA must have a satisfactory compliance evaluation at the time of

approval. We have requested the necessary evaluation from the Office of Compliance.

Sincerely yours,

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

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

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EMAIL: atrixlab@frii.com
http://www.atrixlabs.com

VIA FEDERAL EXPRESS

N/AB

ORIG AMENDMENT

Dale Conner, Director
Office of Generic Drugs
Division of Bioequivalence HFD-650
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

TELEPHONE AMENDMENT

BIOEQUIVALENCE

April 29, 2002

RE: ANDA # 65-112 Erythromycin and Benzoyl Peroxide Topical Gel USP, 3%/5%
Telephone Amendment- Bioequivalence

Dear Mr. Conner:

Atrix Laboratories, Inc. is hereby submitting a telephone amendment to our unapproved Abbreviated New Drug Application for Erythromycin and Benzoyl Peroxide Topical Gel, USP 3%/5% as required by Section 505 (j) of the Federal Food, Drug, and Cosmetic Act, and in accordance with 21 CFR Part 314.96.

Reference is made to voicemail communication from Steve Mazella of FDA, Division of Bioequivalence for Chris French of Atrix Laboratories, Inc. on April 19, 2002.

"Our bioequivalence reviewer has asked me to call you to ask for the following data:

1. First thing is lists of ITT intent to treat population and PP per protocol population patient. The list should include specifics of the two populations; how many started in each one, how many were excluded and then how many finished and then a list of ID for each group of the patients.

2. The second is an appendix 2.3.1 - we don't have it. You refer to it but we don't actually have it here. According to report volume 1.2 page 21, Appendix 2.3.1 should be, should list the evaluable criteria, however, we do not have that appendix.

3. And the third thing is according to volume 1.2 page 19 under the headings of changes in the conduct of the study or planned analysis 5.9.1, 5B you proposed the counter and the correlation for the enter examiner reliability for a lesion should be at least 80%. Can you submit the data on the entry examination correlation?"

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OGD / CDER

Responses to each request is provided as follows:

1. Lists of ITT intent to treat population and PP per protocol population patient are provided in **ATTACHMENT 1.**

2. Appendix 2.3.1, which lists the evaluable criteria, is provided in **ATTACHMENT 2.**

3. In the original bioequivalence analyses of the per-protocol population, Atrix excluded as protocol violations all efficacy data in patients who were evaluated by different examiners at Baseline and Week 12. This resulted in the exclusion of 44 patients from 7 centers. Of these seven centers, only one center (Center 2: _____) had data per the letter of clarification concerning inter-examiner calibration of examiners. Because only one of seven centers had data supporting inter-examiner calibration, Atrix elected to take the conservative approach in the analyses and exclude any patient who did not have the same examiner for both the Baseline and Week 12 evaluations.

   At Center #2 where inter-examiner calibrations were done, three lesion counters were calibrated to a reference lesion counter by counting inflammatory and non-inflammatory lesions on three subjects. A correlation analysis of these data indicate that these examiners are correlated over 80% (see attached results provided in **ATTACHMENT 3**).

   There were 11 patients from this site who were initially excluded. Of these, two (#02080, #02338) were excluded as protocol violations for other reasons, and one was a Vehicle patient (#02076) and was not included in the bioequivalence comparison of the two active treatments. Therefore the remaining eight patients (four in each treatment group) are included in the re-analyses. The result of these re-analyses, including the eight patients, for both the primary and secondary endpoints are contained in the tables provided in **ATTACHMENT 3**.

   For total inflammatory lesions, the original confidence interval was **(0.817,1.161)**. The new confidence interval becomes **(0.833,1.117)**. For the Global Acne Assessment, the original confidence interval was **(0.800,1.087)**. The new confidence interval becomes **(0.817,1.099)**.

This information is submitted for your review and approval. Please acknowledge receipt of this submission by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

Atrix Laboratories, Inc.

Chris L. French
Director, Dermatology Business Unit

Enclosures

2579 MIDPOINT DRIVE
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VIA FEDERAL EXPRESS

NEW CORRESP
NC

Dale Conner, Director
Office of Generic Drugs
Division of Bioequivalence HFD-650
Center for Drug Evaluation and Research
Metro Park North 2, Room 150
7500 Standish Place
Rockville, MD 20855

TELEPHONE AMENDMENT

BIOEQUIVALENCE

May 15, 2002

RE: ANDA # 65-112 Erythromycin and Benzoyl Peroxide Topical Gel USP, 3%/5% Telephone Amendment- Bioequivalence

Dear Mr. Conner:

Atrix Laboratories, Inc. is hereby submitting a telephone amendment to our unapproved Abbreviated New Drug Application for Erythromycin and Benzoyl Peroxide Topical Gel, USP 3%/5% as required by Section 505 (j) of the Federal Food, Drug, and Cosmetic Act, and in accordance with 21 CFR Part 314.96.

Reference is made to a telephone communication between Nina Nwaba of FDA, Division of Bioequivalence and Chris French of Atrix Laboratories, Inc. on May 13, 2002.

Ms. Nwaba stated the reviewer needed the following:

- SAS transport files separated by data type (demography, admission, compliance, adverse events, exclusions, etc.). These files are not compressed (zipped).
- A SAS program that could be used to extract the transport files into SAS data sets.
- Documentation describing each data file and how derived variables were calculated (all contained in the readme.doc file).

This information is submitted for your review and approval. Please acknowledge receipt of this submission by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

Atrix Laboratories, Inc.

Chris L. French
Director, Dermatology Business Unit
Enclosures

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MAY 16 2002
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EMAIL: atrixlab@frii.com
http://www.atrixlabs.com

VIA FEDERAL EXPRESS

ORIG AMENDMENT
N/AM

MINOR AMENDMENT

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

June 19, 2002

RE: ANDA # 65-112 Erythromycin and Benzoyl Peroxide Topical Gel USP, 3%/5%
Minor Amendment- CMC

Dear Mr. Buehler:

Atrix Laboratories, Inc. is hereby submitting an amendment to our unapproved Abbreviated New Drug Application for Erythromycin and Benzoyl Peroxide Topical Gel, USP 3%/5% as required by Section 505 (j) of the Federal Food, Drug, and Cosmetic Act, and in accordance with 21 CFR Part 314.96.

Reference is made to FDA communication dated March 14, 2002.

A response is provided for each deficiency in the order presented in the above referenced communication.

A. Deficiency questions

1. ***FDA comment:*** _____

Atrix response:

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Pages subsequent to page 1 of the firm's
June 19, 2002, letter were unavailable to the redactor.
However, this is not significant as they would have
been withheld from release since the discussion of
chemistry deficiencies carried over from page 1.

A1.1

********** -COMM. JOURNAL- ********** DATE JUL-24-2002 ***** TIME 13:45 ********

MODE = MEMORY TRANSMISSION START=JUL-24 13:44 END=JUL-24 13:45

FILE NO.=934

STN NO.	COMM.	ABBR NO.	STATION NAME/TEL NO.	PAGES	DURATION
001	OK	#	919704829735	004/004	00:00:33

-FDA CDER OGD CHEMI -

********** - ***** - *********

ANDA 65-112

OFFICE OF GENERIC DRUGS

Food and Drug Administration
HFD-600, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Fax: 301-594-0180

FAX TRANSMISSION COVER SHEET

TO: APPLICANT: Atrix Laboratories, Inc. TEL: 970-482-5868 ext. 373

ATTN: Chris L. French FAX: 970-482-9735

FROM: Sarah Ho PROJECT MANAGER: 301-827-5848

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated November 30, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Erythromycin and Benzoyl Peroxide Topical Gel USP, 3%-5% (Erythromycin 3% - Benzoyl Peroxide 5% topical gel).

SPECIAL INSTRUCTIONS:
Labeling comments provided.

ANDA 65-112

OFFICE OF GENERIC DRUGS

Food and Drug Administration
HFD-600, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
Fax: 301-594-0180

FAX TRANSMISSION COVER SHEET

TO: APPLICANT: Atrix Laboratories, Inc. TEL: 970-482-5868 ext. 373

ATTN: Chris L. French FAX: 970-482-9735

FROM: Sarah Ho PROJECT MANAGER: 301-827-5848

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated November 30, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Erythromycin and Benzoyl Peroxide Topical Gel USP, 3%-5% (Erythromycin 3% - Benzoyl Peroxide 5% topical gel).

SPECIAL INSTRUCTIONS:
Labeling comments provided.

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

ANDA Number: 65-112

Date of Submission: November 30, 2001

Applicant's Name: Atrix Laboratories, Inc.

Established Name: Erythromycin and Benzoyl Peroxide Topical Gel USP, 3%-5%.
[Erythromycin 3% - Benzoyl Peroxide 5% topical gel]

Labeling Deficiencies:

1. CONTAINER:

   a. Erythromycin: 0.8 g and 1.6 g

      i. Revise to read, "Net Wt. ___ grams active erythromycin".

      ii. Print the text, "Prior to ... erythromycin" in bold print and add the text **"TO THE PHARMACIST: IMPORTANT"** in bold uppercase print immediately prior to this statement.

      iii. Increase the prominence of the statement, **"Not for separate dispensing".**

   b. Erythromycin and Benzoyl peroxide topical gel: 23.3 g and 46.6 g

      i. Front panel

         A. Delete " —— " and add the text,"Topical gel: erythromycin (3%), benzoyl peroxide (5%)" immediately beneath the established name.

         B. Add the text "Net Wt." prior to "___ grams (as dispensed)".

         C. Prior to the text, "After ... and fragrance" add the word **"Description -".**

         D. Indicate the percentage of alcohol. We refer you to 21 CFR 201.10(d)(2).

      ii. Side panel

         A. Increase the prominence of the text appearing on the side panel, [except the text, "KEEP ... CHILDREN"].

         B. Delete the extra spaces appearing in the text of the third paragraph.

2. CARTON: 23.3 g and 46.6 g

   i. See comments 1(b)(i)(A and D) under CONTAINER.

   ii. Side panels flaps: **TO THE PHARMACIST**

Print the text: **"room temperature ETHYL ALCOHOL (70%)"** in bold print.

iii. Side panel

Increase the prominence of the text printed on the side panel, [except the text, "KEEP ... CHILDREN"].

iv. When printing final print, indicate the location of the lot number and expiration date.

3. INSERT

a. TITLE

i. Delete " —— " following the established name and add the text, "Topical gel: erythromycin (3%), benzoyl peroxide (5%)" between the established name and the **"Rx"** symbol.

ii. Immediately following the **"Rx"** symbol, add a red box with the following text printed in red:

PLEASE READ COMPLETE COMPOUNDING DIRECTIONS
NOTE: TAP UNTIL ALL POWDER FLOWS FREELY. ADD ETHYL ALCOHOL (70%) TO VIAL (TO THE MARK) AND **IMMEDIATELY** SHAKE/DISSOLVE **COMPLETELY.**

iii. Following the red box print **"For Dermatologist Use Only – Not for Ophthalmic Use"** in bold print and "Reconstitute Before Dispensing" in bold red print.

b. DESCRIPTION

i. Add "USP" following the established name in the first sentence.

ii. We note that you list———————— in your component statement. However, it is not listed in your list of inactive ingredients in the DESCRIPTION section. Please comment.

c. HOW SUPPLIED

i. Revise to read as follows:

TO THE PHARMACIST: IMPORTANT – Prior to dispensing, tap ...

ii. In this section, we encourage you to include a statement indicating that a spatula is supplied for mixing the drug product.

Please revise your container labels and carton and insert labeling, as instructed above, and submit in final print.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes - http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

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

APPEARS THIS WAY
ON ORIGINAL

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

ATRIX
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PHONE: (970) 482-5868
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EMAIL: atrixlab@frii.com
http://www.atrixlabs.com

VIA FEDERAL EXPRESS

N/A F
ORIG AMENDMENT

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

FAX LABELING AMENDMENT

August 7, 2002

RE: ANDA # 65-112 Erythromycin and Benzoyl Peroxide Topical Gel USP, 3%/5%
FAX Amendment- Labeling

Dear Mr. Buehler:

Atrix Laboratories, Inc. is hereby submitting an amendment to our unapproved Abbreviated New Drug Application for Erythromycin and Benzoyl Peroxide Topical Gel, USP 3%/5% as required by Section 505 (j) of the Federal Food, Drug, and Cosmetic Act, and in accordance with 21 CFR Part 314.96.

Reference is made to FDA fax labeling communication dated July 24, 2002.

All labeling changes have been made as requested. 12 copies of final print labeling are provided.

3.b.ii Comment: *We note that you list* [redacted] *in your component statement. However, it is not listed in your list of inactive ingredients in the DESCRIPTION section. Please comment.*

Response: [redacted] is the fragrance inactive ingredient. Atrix choose to use the general term fragrance, as seen in the innovator labeling.

This information is submitted for your review and approval.

Please acknowledge receipt of this submission by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

Atrix Laboratories, Inc.

Chris L. French
Director, Dermatology Business Unit

Enclosures

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FORT COLLINS, CO 80525-4417
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FAX: (970) 482-9735
http://www.atrixlabs.com

VIA FAX

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

TELEPHONE AMENDMENT

September 30, 2002

RE: ANDA # 65-112 Erythromycin and Benzoyl Peroxide Topical Gel USP, 3%;5% Telephone Amendment- CMC

Dear Mr. Buehler:

Atrix Laboratories, Inc. is hereby submitting an amendment to our unapproved Abbreviated New Drug Application for Erythromycin and Benzoyl Peroxide Topical Gel USP, 3%;5% as required by Section 505 (j) of the Federal Food, Drug, and Cosmetic Act, and in accordance with 21 CFR Part 314.96.

Reference is made to a phone conversation on September 30, 2002 and September 26, 2002 between FDA and Atrix Laboratories, Inc.

On September 26, 2002 FDA relayed the following two deficiency issues in regard to the Chemistry, Manufacturing and Controls section of the above referenced ANDA.

1. The specification for Erythromycin API needs to include a test for ————
2. The Chemistry Reviewer is not sure that our delayed use drug product assay method is stability indicating with respect to erythromycin.

On September 30, 2002, Atrix called FDA for clarification on issue #2. After discussions between FDA and Atrix, the following response to both issues is provided.

1. Please find attached a revised specification sheet that has been modified to include the test for _____ as requested.

2. [redacted]

This information is submitted for your review and approval. Please acknowledge receipt of this submission by signing and dating the enclosed copy of the cover letter and returning it in the self-addressed stamped envelope.

Sincerely,

Atrix Laboratories, Inc.

Chris L. French
Director, Dermatology Business Unit
Enclosures

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

ATRIX
LABORATORIES, INC.

PHONE: (970) 482-5868
FAX: (970) 482-9735
http://www.atrixlabs.com

VIA FAX

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

TELEPHONE
AMENDMENT
ORIG AMENDMENT

October 14, 2002

RE: ANDA # 65-112 Erythromycin and Benzoyl Peroxide Topical Gel USP, 3%;5%
Telephone Amendment- CMC

Dear Mr. Buehler:

Atrix Laboratories, Inc. is hereby submitting an amendment to our unapproved Abbreviated New Drug Application for Erythromycin and Benzoyl Peroxide Topical Gel USP, 3%;5% as required by Section 505 (j) of the Federal Food, Drug, and Cosmetic Act, and in accordance with 21 CFR Part 314.96.

Reference is made to a phone conversation on October 7, 2002 between FDA and Atrix Laboratories, Inc.

FDA chemistry reviewer informed us that even after submission of our telephone amendment of September 30, 2002 upper management still had concerns.

Discussions were centered on the issue of testing erythromycin for delayed use drug product. FDA

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10/14/2002 ATRIX LETTER

2579 MIDPOINT DRIVE
FORT COLLINS, CO 80525-4417
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http://www.atrixlabs.com

VIA EXPRESS MAIL

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

UNSOLICITED AMENDMENT

NEW CORRESP
NC

2/25/04

November 25, 2002

RE: ANDA # 65-112 Erythromycin and Benzoyl Peroxide Topical Gel USP, 3%;5% Unsolicited Amendment- CMC

Dear Mr. Buehler:

Atrix Laboratories, Inc. is hereby submitting an amendment to our unapproved Abbreviated New Drug Application for Erythromycin and Benzoyl Peroxide Topical Gel USP, 3%;5% as required by Section 505 (j) of the Federal Food, Drug, and Cosmetic Act, and in accordance with 21 CFR Part 314.96.

Please note that as of November 21, 2002, Atrix Laboratories, Inc does not longer employ Chris French. Kathy Coressel will now be assuming the responsibility of signing all correspondences. Please direct all correspondence to Kathy Coressel.

Kathy Coressel can be reached by phone at (970) 212-4834.
The fax number will remain the same, (970) 482-9735.

Thank you in advance for your cooperation and we are sorry for any inconvenience.

Sincerely,

Atrix Laboratories, Inc.

Kathy Coressel

Kathy Coressel
Regulatory Project Leader

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

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LABORATORIES, INC.

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VIA EXPRESS MAIL

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

NOTE 4-28-03

UNSOLICITED AMENDMENT

NEW CORRESP

April 17, 2003

RE: ANDA 65-112 Erythromycin and Benzoyl Peroxide Topical Gel USP, 3%;5% Unsolicited Amendment - Change in signature responsibility.

Dear Mr. Buehler:

Atrix Laboratories, Inc. is hereby submitting an amendment to our unapproved Abbreviated New Drug Application for Erythromycin and Benzoyl Peroxide Topical Gel USP, 3%;5% as required by Section 505 (j) of the Federal Food, Drug, and Cosmetic Act, and in accordance with 21 CFR Part 314.96.

Atrix Laboratories, Inc. has hired a Vice President of Regulatory Affairs, Cheri Jones. Ms. Jones will now be assuming the responsibility of signing all correspondences. Please direct all correspondence to Cheri Jones.

Cheri Jones can be reached by phone at (970) 212-4901.
The fax number will remain the same, (970) 482-9735.
Email is cjones@atrixlabs.com.

Thank you in advance for your cooperation and we are sorry for any inconvenience.

Sincerely,

Cheri Jones, M.S., RAC
Atrix Laboratories, Inc.
Vice President Regulatory Affairs

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ANDA 65-112

AUG 26 2003

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

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated November 30, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Erythromycin and Benzoyl Peroxide Topical Gel USP, 3%/5%.

Reference is also made to your amendments dated April 29, June 19, August 7, and October 14, 2002.

We have completed the review of this abbreviated application and have concluded that it is not approvable under Section 505 of the Act. Specifically, we have concluded that the bioequivalence studies you have submitted fail to demonstrate that your drug product is bioequivalent to the reference listed drug product (RLD), Benzamycin Topical Gel of Dermik Laboratories, as required under 21 CFR 314.127(a)(6)(i).

We have the following comments:

Your data fail to demonstrate that Atrix Laboratories, Inc.'s Erythromycin-Benzoyl Peroxide Topical Gel USP, 3%/5%, is bioequivalent to Benzamycin® Topical Gel. Your data use the accepted primary endpoint of percent reduction from baseline in all lesion counts (inflammatory, non-inflammatory, and total) at week 12, and the dichotomized (success/failure) analysis of the Physician Global Assessment.

Furthermore, since a previous New Drug Application (NDA) for erythromycin-benzoyl peroxide topical gel was approved based upon 8-week studies, we also analyzed the 8-week data in your

application. These data also fail to meet the accepted bioequivalence criteria.

The presence of a comedone (non-inflammatory lesion) is a clinical hallmark of acne vulgaris. The agency will not approve drug products for this indication without the applicant/sponsor having to demonstrate effectiveness for both inflammatory and non-inflammatory lesions. Thus, it is important for a generic formulation also to demonstrate effectiveness for both lesion types within the bioequivalence limits.

As a result of our determination, the Office of Generic Drugs has suspended all further review of this application. Substantive review may resume upon your submission of an amendment described below containing complete information and data necessary to demonstrate that your drug product is bioequivalent to the RLD.

The file on this ANDA is now closed. You are required to take an action described under 21 CFR 314.120 and 21 CFR 314.96, in which you state your intent either to amend or withdraw this application. Should you decide to amend this application, the amendment should respond to all of the bioequivalence deficiencies stated above. Please note that in the event you need to reformulate your drug product to meet the bioequivalence requirements, your amendment will also need to include updated chemistry, manufacturing, controls and labeling information. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. Should you choose to amend this application, the amendment will be classified as a "Major Amendment", which should be clearly designated in your cover letter. Your cover letter should also clearly highlight the categories of information included in the submission; i.e., chemistry, bioequivalence, and/or labeling.

If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

If you have further questions concerning the status of this application, please contact the project manager, Ann Vu, R.Ph., at (301) 827-5848. Please include a copy of this letter as part of any future correspondence on this application.

Sincerely yours,

Gary Buehler 8/26/03
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 65-112
DUP Jacket
Division File
Field copy
HFD-600/G.Buehler
HFD-650/D.Conner
HFD-610/R.West

Endorsements:
HFD-629/G.Kang/ N/for R.K 8/21/03
HFD-623/J.Fan/ for GK 8/21/03
HFD-617/T.Vu/ 8/21/03
HFD-650/D Conner/ 8/21/03
HFD-617/T Ames/ 8/25/03
HFD-600/ D.Hixon / ORA 8/25/03

Robert Lyn Lutt 8/26/2003

F/T by:

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FATAL FLAW LETTER - NOT APPROVABLE - MAJOR

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*NOT ADMITTED IN DC

DIRECT DIAL (202) 737-7551

September 5, 2003

BY FACSIMILE/CONFIRMATION COPY BY MAIL

Gary Buehler, R.Ph.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
HFD-600
Room 286
Rockville, Maryland 20855

Re: ANDA 65-112, Atrix Laboratories, Inc., Erythromycin and Benzoyl Peroxide Topical Gel USP, 3%, 5%

Dear Mr. Buehler:

On behalf of and as counsel to Atrix Laboratories, Inc. (Atrix) and referencing a conversation today with the project manager on ANDA 65-112, Ms. Ann Vu, we are notifying you that Atrix will be pursuing dispute resolution in accordance with either the draft Guidance for Industry, Formal Dispute Resolution: Appeals Above the Division Level or 21 C.F.R. § 314.103. This request for dispute resolution will occur within 180 days of the date of the not approvable letter as required by 21 C.F.R. § 314.120(b).

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If you have any questions, please feel free to contact me at (202) 737-7551.

Sincerely,

Michelle L. Butler

MLB/cld
Enclosure

cc: Cheri Jones, Atrix Laboratories, Inc.

65-112
3.1

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*NOT ADMITTED IN DC

November 4, 2003

BY FEDERAL EXPRESS

NEW CORRESP
NC

Mr. Gary J. Buehler
Director
Office of Generic Drugs
Food and Drug Administration (HFD-600)
Center for Drug Evaluation and Research
7500 Standish Place, Room 286
Rockville, Maryland 20855

Re: Formal Dispute Resolution Request
Abbreviated New Drug Application 65-112
Erythromycin – Benzoyl Peroxide Topical Gel USP, 3%/5%

Dear Mr. Buehler:

Hyman, Phelps & McNamara, P.C. is submitting this request for formal dispute resolution on behalf of Atrix Laboratories, Inc. ("Atrix"). This request is based on procedural and scientific grounds. A copy of this request will be submitted to Abbreviated New Drug Application ("ANDA") 65-112.

On August 26, 2003, Atrix received notification from the Office of Generic Drugs ("OGD") that its ANDA for Erythromycin-Benzoyl Peroxide Topical Gel USP, 3%/5% ("EBP Gel") was not approved based on OGD's determination that EBP Gel ("test drug") was not bioequivalent to the reference drug.

Atrix believes that data submitted in ANDA 65-112 established that EBP Gel is bioequivalent to the reference drug and should be approved. Bioequivalence was established based on a comparison of primary clinical endpoints identified in the study

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protocol.[1] Both the percent reduction of inflammatory lesions and Global Assessment fell within OGD's standard confidence limits of 80 to 125% and were superior to vehicle. As recommended by OGD, the study endpoints and analyses were based on endpoints used by FDA for approval of the reference drug, and on Atrix's interpretation of comments on its draft protocol that were provided by OGD on September 27, 2000.

OGD's determination that EBP Gel was not bioequivalent is based on comparisons of secondary endpoints that were not required for approval of the reference drug. Atrix believes that OGD's non-approval of ANDA 65-112 is contrary to the intent and requirements of subsection 505(j) of the Federal Food, Drug and Cosmetic Act ("FDC Act") and agency precedent. Furthermore, reanalysis of data that were submitted in ANDA 65-112, using the same database of efficacy evaluable subjects with the exclusion of one highly influential data point, establishes that EBP Gel is at least as good as the reference drug. This is true whether the primary inflammatory lesion endpoints (where bioequivalence has been established) or the secondary non-inflammatory and total lesions endpoints cited in the not approvable letter are evaluated for bioequivalence. Based on this further analysis and agency precedent, EBP Gel should be approved.

I. Facts

On March 13, 2000, pursuant to 21 C.F.R. §320.22(b)(3), Atrix submitted a request to FDA for a waiver from the requirement for the submission of evidence demonstrating the in vivo bioequivalence of EBP Gel to the reference drug. On May 8, 2000, Atrix received OGD's denial of this request.[2] OGD stated that the gel was not a true solution in that the solubilized mixture of drug and alcohol was only suspended in the gel.[3] Atrix was directed to conduct an in vivo bioequivalency study with clinical endpoints, and to submit a draft protocol for review.

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1 Atrix Clinical Study No. BEN0002, "A 12-Week, Multicenter, Double-Blind, Randomized, Parallel Study Comparing Benzamycin® (Dermik Laboratories, Inc.), Erythromycin-Benzoyl Peroxide Topical Gel USP (Atrix Laboratories, Inc.), and Vehicle Control for the Treatment of Acne Vulgaris" (Dec. 2000).

2 FDA letter from Gary J. Buehler, Acting Director, OGD, to Robert Nelson, Atrix Laboratories, Inc., (rec'd May 8, 2000) ("FDA May 8, 2000 letter").

3 In contrast, FDA granted a waiver of in vivo bioequivalence for Erythromycin Topical Gel USP 2%, ANDA 64-184, in 1997. The reference listed drug ("RLD") for this product was approved by FDA in 1987. As with EBP Gel, the

(continued . . .)

Atrix promptly contacted OGD to determine the requirements for a bioequivalency study with clinical endpoints. Atrix was told in a conversation with an OGD official that because there was no guidance document available, Atrix should review the medical and statistical reviews of the reference product's NDA for appropriate clinical endpoints and use a statistically based plan to determine the appropriate number of patients.[4] Atrix was also told that the study should contain three treatment arms, including a vehicle arm.[5]

Following FDA's direction, Atrix reviewed the summary basis of approval ("SBA") for the reference drug, Benzamycin Gel (Erythromycin 3% and Benzoyl Peroxide 5%). Approval of that product was based on reductions in the counts of inflammatory lesions. FDA stated in the SBA that "the inflammatory lesion count best measures the effectiveness of a product of this type."[6] Approval was based on two 10-week studies.[7] One pivotal study used the product formulation that was approved and enrolled 120 patients in four parallel groups. The second pivotal trial, which used a product formulation different from that approved,[8] enrolled 84 patients assigned to four parallel groups. In total, fewer than 50 patients in the two pivotal trials received Benzamycin. Approval was based on the percent reduction of inflammatory lesions from baseline for each treatment group at each return visit.

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erythromycin gel products are a solubilized mixture of drug and alcohol and are suspended in the gel.

4 Atrix record of telephone call between Robert Nelson at Atrix and Patty Ngyuen of OGD on May 15, 2000 (attached as Exhibit 1).

5 In contrast, FDA approved ANDAs for Permethrin Lotion 1% for treatment of head lice and Permethrin Cream 5% for treatment of scabies with no vehicle arm.

6 Benzamycin Topical Gel, NDA 50-557, Summary Basis of Approval, at 3 (Oct. 9, 1984).

7 There were also two supportive studies.

8 The tested formulation contained [redacted] which was removed from the marketed products.

Based on its analysis of the SBA, Atrix submitted on June 7, 2000, to OGD a draft protocol to establish the bioequivalency of EBP Gel to the reference drug. Up to 300 patients would be randomized into three arms – reference, test drug, and vehicle control (instead of a placebo) – in a 3:3:1 ratio. Clinical bioequivalence was to be established if the ratio of the mean week 10 total inflammatory lesion count for the test treatment group to the reference treatment group fell within OGD's standard confidence limit of 80 to 125%. In addition, the draft protocol required measurement of secondary endpoints to include overall severity grade and the number of non-inflammatory and total lesions.

OGD responded on September 27, 2000. OGD recommended a 12-week study rather than a 10-week study. The recommended primary endpoints were lesion counts and Investigator's Global Assessment. The letter also stated that "[l]esion counts should be presented as follows for inflammatory, non-inflammatory, and total lesions: 1) Baseline and Endpoint lesion counts, 2) mean reduction in lesion counts from baseline to endpoint, and 3) mean percentage reduction in lesion counts form [sic] baseline to endpoint."[9] Consistent with OGD's earlier advice, Atrix interpreted this to mean that Global Assessment was to be a primary endpoint in addition to inflammatory lesions. The letter did not state that all the measurements that Atrix considered secondary must be within the 80 to 125% confidence limits for EBP Gel to be considered bioequivalent to the RLD. The letter stated that to be considered bioequivalent, the test and reference drug not only had to perform the same, both drugs had to perform better than the vehicle.

Atrix revised the draft protocol based on the guidance from OGD. Atrix extended the trial to 12 weeks and increased the size of the study to about 360 subjects randomized into three arms in a 2:2:1 ratio. Consistent with OGD's recommendation to refer to the Benzamycin SBA, the Investigator's Global Assessment was designated a primary endpoint, along with inflammatory lesions. Secondary endpoints were non-inflammatory lesions and total lesions, which would be analyzed as recommended by OGD. Importantly, it was Atrix's understanding that the primary endpoints to establish bioequivalency (i.e., inflammatory lesions and Global Assessment) would be sufficient to establish bioequivalence. This understanding was based on FDA's analysis of inflammatory lesions when Benzamycin was approved.[10]

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9 FDA letter from Dr. Dale Conner, OGD, to Robert Nelson, Atrix Labs., Inc., at 2 (Sept. 27, 2000).

10 An FDA official noted in a contact with Atrix that, when looking back at the September 27, 2000 letter Atrix received from FDA during review of Atrix's

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Following revision of the protocol, the study was conducted.[11] ANDA 65-112 was submitted to OGD on November 30, 2001. Based on the precedent set for the reference drug and Atrix's interpretation of OGD's guidance, the same primary endpoints as used in approval of the reference product were analyzed. EBP Gel was demonstrated to be bioequivalent to the reference drug.[12] Mean percentage reduction in lesion counts was the primary analysis. Both EBP Gel and Benzamycin met the additional requirement of being superior to vehicle.[13] As shown in Table E in the final study report, EBP Gel was not uniformly within the 80 to 125% confidence limits for all other analyses and measurements considered by Atrix to be secondary.[14] Deviations from the 80 to 125% confidence limits occurred primarily because of differences in effectiveness for treating non-inflammatory lesions for which neither EBP Gel nor Benzamycin was superior to vehicle. Deviations from confidence limits suggested that EBP Gel performed better (but not significantly) than the reference drug in reducing non-inflammatory lesions. As

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protocol, it was recognized that it was perhaps not made as clear as it should have been that FDA would require bioequivalence on all three lesion categories (inflammatory, non-inflammatory, and total). The FDA official also noted that she hoped that this experience would help FDA provide more clear advice during the protocol review process in the future.

11 After the study was conducted and statistical analyses were completed, Atrix received a letter dated October 23, 2001 from Dr. Dale Conner that responded to questions asked by Atrix on August 28, 2001. This letter stated: "Bioequivalence will be established if all the primary efficacy measurements show statistical equivalence using the 90% confidence interval criteria that was included in the letter dated September 27, 2000."

12 See Table B (attached as Exhibit 2) from the Atrix Laboratories, Inc. Report BEN0002, "A 12-Week, Multicenter, Double-Blind, Randomized, Parallel Study Comparing Benzamycin® (Dermik Laboratories, Inc.), Erythromycin-Benzoyl Peroxide Topical Gel USP (Atrix Laboratories, Inc.), and Vehicle Control for the Treatment of Acne Vulgaris" (Nov. 30, 2001).

13 See id., Table C (attached as Exhibit 3).

14 See id., Table E (attached as Exhibit 4).

shown in Table F to the final study report, except for non-inflammatory lesions, both EBP Gel and the reference drug were better than the vehicle in most analyses.[15]

On August 26, 2003, OGD issued a letter stating that EBP Gel was not shown to be bioequivalent to the reference drug. OGD also stated:

> The presence of a comedone (non-inflammatory lesion) is a clinical hallmark of acne vulgaris. The agency will not approve drug products for this indication without the applicant/sponsor having to demonstrate effectiveness for both inflammatory and non-inflammatory lesions. Thus, it is important for a generic formulation also to demonstrate effectiveness for both lesion types within the bioequivalence limits.[16]

In the case of the reference drug, this was not true. The reference drug, Benzamycin, was not required to demonstrate effectiveness in treating non-inflammatory lesions as part of its approval. The Medical Officer's review of the supplement states that: "[t]he reductions in papule and pustule counts are the best indicators of clinical improvement in the evaluation of topical anti-microbial acne agents."[17] Additionally, FDA has approved drugs for the treatment of acne where the drug has been more effective than vehicle on two out of the three lesion counts, i.e., inflammatory, non-inflammatory, and total.

II. Discussion

A. Subsection 505(j) Of The FDC Act Is Intended To Simplify And Speed Approval Of Low Cost Generic Drugs

Title 1 of the Drug Price Competition and Patent Term Restoration Act of 1984 is subsection 505(j) of the FDC Act and establishes the ANDA path to new drug approval.

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15 See id., Table F (attached as Exhibit 5).

16 FDA letter from Gary Buehler, Director, OGD, to Cheri Jones, Atrix Labs., Inc., at 2 (Aug. 26, 2003) ("FDA Aug. 26, 2003 letter").

17 Benzamycin Topical Gel, NDA 50-557, Medical Officer Review of Supplement, at 1 (Aug. 9, 1983).

The hallmark of an ANDA is that the applicant must establish the new drug is bioequivalent to the reference listed drug.[18] As stated in the House Report Part 1, which is part of the legislative history preceding enactment of subsection 505(j):

> The only difference between a NDA and an ANDA is that the generic manufacturer is not required to conduct human clinical trials. FDA considers such retesting to be unnecessary and wasteful because the drug has already been determined to be safe and effective. Moreover, such retesting is unethical because it requires that some sick patients take placebos and be denied treatment known to be effective.[19]

Importantly, because safety and effectiveness is a given, FDA is not permitted to require anything more than information establishing bioequivalency to approve an ANDA.[20] A drug shall be considered to be bioequivalent if the "rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug . . . ."[21] Although the statute defines bioequivalence, it does not define what type of information will be sufficient to show that a drug is bioequivalent. Congress left that determination to FDA. If a waiver of evidence for in vivo bioequivalence is not granted, the typical way that bioequivalency is demonstrated is using a crossover study in a limited number of patients (24-36), in which the active moiety or the active metabolite of the test and reference drug are measured in the appropriate biological fluid (e.g., blood, serum, plasma).[22] If the comparison of levels of the active moiety or metabolite for the test and reference drugs are within reasonable limits (80 to 125% at the 90% confidence interval), they are considered bioequivalent.

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18 See FDC Act § 505(j)(2)(A)(iv); 21 U.S.C. § 355(j)(2)(A)(iv).

19 H.R. Rep. No. 98-857, pt.1, at 16 (1998), reprinted in Allan M. Fox and Alan R. Bennett, "Legislative History of the Drug Price Competition and Patent Term Restoration Act of 1984," Section 6, at 16 (1987).

20 See FDC Act § 505(j)(2)(A); 21 U.S.C. § 355 (j)(2)(A).

21 Id. § 505(j)(8); 21 U.S.C. § 355(j)(8).

22 See 21 C.F.R. § 320.24(b)(1).

For some products, such testing is not possible because biological fluid concentrations are not an accurate measure of drug availability at the site of activity. For these products, well-controlled clinical studies with clinical endpoints can be used to establish bioequivalence.[23]

Topical products for the treatment of acne vulgaris are prime examples of products for which the typical active moiety or metabolite concentration study cannot be done. For these products, a waiver of bioequivalency study may be granted. In the alternative, FDA has also required a well-controlled study with clinical endpoints. As recognized by FDA, studies involving clinical endpoints are "the least accurate, sensitive and reproducible of the general approaches for determining . . . bioequivalence."[24] Paradoxically, and inconsistent with Congress's intent when enacting the Drug Price Competition and Patent Term Restoration Act of 1984, clinical endpoint studies may require more patients, take longer, and be more expensive than the typical pharmacokinetic study. Indeed, such studies may require more subjects to be treated with the test drug than were treated with the approved reference drug.[25]

FDA has broad discretion to determine how bioequivalence is to be demonstrated. FDA's discretion is not without limits, however. "Although the FDA has wide discretion to determine how the bioequivalence requirement is met, its discretion must be based on a reasonable and scientifically supportable criterion, whether it chooses to do so on a case-by-case basis or through more general inferences about a category of drugs . . . ."[26] And, FDA's determination of whether bioequivalence was adequately demonstrated has

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23 See id. § 320.24(b)(4).

24 Id.

25 For example, only 47 patients actually received the RLD in the two 10-week pivotal studies that supported its approval. In a single multicenter 12-week study, 140 patients received EBP Gel and 142 patients received Benzamycin in the study that Atrix submitted to establish bioequivalency to the RLD, Benzamycin. Because of the size of the study, the Atrix study may actually have provided more reliable evidence of the safety and effectiveness of Benzamycin than did the studies supporting its approval.

26 Bristol-Myers Squibb Co. v. Shalala, 923 F. Supp. 212, 218 (D.D.C. 1996).

been remanded for further review where FDA failed to "cogently explain" its conclusion.[27]

In the present instance, FDA has the discretion to decide that EBP Gel is bioequivalent to Benzamycin. For example:

- FDA could decide that Atrix followed the advice of OGD and established the bioequivalency of EBP Gel to the reference drug based on the primary endpoints identified in the reference drug approval.
- FDA could determine that its requirement to show bioequivalence for the test drug to the reference drug, and also superiority for both the reference and test drug to the vehicle is unnecessary and contrary to the intent of Section 505(j)(2)(A) of the FDC Act.
- FDA could decide that insistence on a confidence interval of 80 to 125% is unnecessary and inappropriate for a study with a parallel rather than a crossover study design.[28]

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27 A.L. Pharma, Inc. v. Shalala, 62 F.3d 1484, 1492 (D.C. Cir. 1995).

28 FDA is well aware that the 80 to 125% confidence interval may be unduly restrictive for parallel study designs due to the inherently higher intersubject variability than occurs in an intrasubject crossover study. At the March 12, 2003 Pharmaceutical Science Advisory Committee Meeting, an FDA consultant, Dr. Jurgen Venitz questioned the validity of applying the 80 to125% confidence interval to a parallel rather than a crossover study design. He said that there was no "magic" to the 80 to 125% interval even in PK studies and that here FDA is applying it "in a level above the PK." Dr. Venitz said that the 80 to 125% interval assumes a crossover design and is therefore too strict for the clinical endpoint bioequivalence study. Dr. Venitz also said, "I don't see any rationale why you shouldn't be able to flexibility [sic] use criteria that are more appropriate based on the endpoint that you have and what's considered to be clinically significant." Advisory Committee Transcript for Pharmaceutical Science, at 204-205 (Mar. 12, 2003) ("2003 Advisory Committee Transcript").

Whether strict adherence to the 80-125% confidence interval is always necessary also arose in discussions at an earlier meeting of FDA's Advisory Committee for

(continued . . .)

- FDA could determine that requiring that all measured endpoints be within the 80 to 125% confidence interval is unnecessary to establish bioequivalence when the approval of the reference drug was based on effectiveness for inflammatory lesions only.

- FDA could determine that evidence that the EBP Gel is at least as good as the reference drug is consistent with agency precedent and establishes bioequivalence.

- FDA could determine that ANDA precedents for other topical products including acne drug products, in which clinical results act as "surrogates" for pharmacokinetic comparisons should have different "goal posts" for approval.

- FDA could decide that a generic drug should not be held to a higher effectiveness standard than is currently required for an innovator drug.

It is within FDA's discretion to reach any of these conclusions and approve ANDA 65-112. Conversely, if FDA maintains that EBP Gel is not bioequivalent to the reference drug, it should "cogently explain" the basis for its decision and how that decision is consistent with science, with agency precedent, and with the statute and agency policy to approve safe and effective lower cost generic drug products.

B. Atrix Demonstrated Bioequivalency And Superiority Based On Principal Endpoints Predetermined In The Protocol And Consistent With FDA's Advice

As discussed above, after its request for a waiver of a bioequivalency study was denied, Atrix sought guidance from OGD regarding the design of a well-controlled clinical trial with clinical endpoints. Because OGD did not have a guidance document relevant to topical agents for treatment of acne, Atrix was referred to the SBA for the reference product, Benzamycin. According to the FDA Medical Officer's review, there

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Pharmaceutical Science, in the context of the committee's review of the dermatopharmacokinetic (DPK) approach and related issues. See Advisory Committee for Pharmaceutical Science Meeting Transcript, at 59-60, 131, and 139 (Nov. 29, 2001).

were two pivotal trials. There were a total of 111 evaluable patients in one four-arm parallel study and 75 patients in the other. A total of 47 patients received the reference drug and were efficacy evaluable. The FDA reviewer relied on papule and pustule counts (inflammatory lesions) as the "best indicators of clinical improvement in the evaluation of topical anti-microbial acne agents."[29] The statistical analysis was based on percent reduction from baseline.

Atrix submitted a draft protocol based on the reference drug SBA. The primary endpoint was inflammatory lesion counts, and the study was powered to show bioequivalence based on total inflammatory lesion counts.

Based on comments from OGD, Atrix revised the protocol to make Investigator's Global Assessment a primary endpoint, to expand the trial to 12 weeks, and to increase the number of study participants. The comments from OGD stated that Atrix should present inflammatory lesion counts, non-inflammatory lesion counts, and total lesion counts. Statistical analyses should be done based on total counts, mean reduction in lesion counts, and percent reduction in lesion counts. Because all these analyses were not required for the reference drug, Atrix understood this request to be a statement of additional supportive analyses rather than a requirement that EBP Gel be shown to be bioequivalent (i.e., within the 80 to 125% confidence interval) for all these additional analyses as well as superior to vehicle in each comparison.

As a result of Atrix's understanding of OGD's comments, the study was powered to show bioequivalence based on inflammatory lesion counts and Investigator's Global Assessment. Altogether, 352 subjects were enrolled – 140 for EBP Gel, 142 for Benzamycin, and 70 for vehicle. Slightly more than three times as many patients received Benzamycin in the Atrix trial (142) as were evaluable in the two pivotal Benzamycin trials (47) that led to the reference product's approval. Although the Atrix bioequivalence study was far larger than the pivotal trials for Benzamycin, it was not powered statistically to show bioequivalence for non-inflammatory lesions, because this was not believed to be a requirement. Further, to calculate the size of a study in order to have appropriate statistical power, it is necessary to have reliable estimates of the intersubject variability and an estimate of the mean effectiveness of the test drug. There was not sufficient information in the Benzamycin SBA or available published literature to

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[29] Benzamycin Topic Gel, NDA 50-557, Medical Officers' Review of Supplement, at 2 (Aug. 9, 1983).

make such a calculation. It is known, however, that variability in effectiveness for non-inflammatory lesions is much greater than for inflammatory lesions, in part because of the difficulty in assessing non-inflammatory lesions numerically. To power a study to demonstrate bioequivalence for non-inflammatory lesions within the confidence limits customary for crossover studies would have required a sample size that was prohibitive and clearly contrary to the intent of Congress to simplify the availability of generic drug products.

Based on the percent reduction of inflammatory lesions and Global Assessment Scores, EBP Gel and the reference drug, Benzamycin, have been proven to be bioequivalent.[30] Additionally, the percent reduction of inflammatory lesions and Global Assessment Scores were statistically significantly better than vehicle.[31] The percent reduction of total lesions for both EBP Gel and the RLD were significantly better than vehicle.[32] Not all comparisons of secondary endpoints and analyses fell within the 80 to 125% confidence interval. Although neither EBP Gel nor Benzamycin were statistically significantly better than vehicle at treating non-inflammatory lesions, EBP Gel appeared to be numerically better than Benzamycin when analyzed for mean percent reduction from baseline (0.606, 1.960) and mean reduction from baseline (0.631, 1.479). A comparison of mean non-inflammatory lesion counts (0.839, 1.124) fell within the standard confidence intervals that are used for crossover studies.[33] In any event, and consistent with agency precedent, OGD should not deny approval where a generic drug performs at least as good as the reference drug.

Because of the differences noted in non-inflammatory lesions, the comparison for mean percent reduction from baseline for total lesions fell just outside the confidence interval (0.858, 1.292), which suggests that EBP Gel is no worse than and possibly more effective than Benzamycin. However, analyses of total lesions through mean lesion counts and mean reduction from baseline fell within the standard bioequivalence confidence intervals of 80 to 125%. Moreover, the mean percent reduction from baseline

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30 See Exhibit 2, *supra* note 12.

31 See Exhibit 3, *supra* note 13.

32 See Exhibit 5, *supra* note 15.

33 See Exhibit 4, *supra* note 14.

analysis of total lesions demonstrated that both EBP Gel and Benzamycin were statistically significantly superior to vehicle.

In summary, EBP Gel demonstrated bioequivalence to the reference drug based on a comparison of effectiveness in reducing inflammatory lesions and in Global Assessment, the primary endpoints in the bioequivalency study. Additionally, both EBP Gel and Benzamycin were superior to vehicle on this basis. Analyses of secondary endpoints are consistent and supportive of bioequivalency. Accordingly, ANDA 65-112 should be approved.

C. Reanalysis Of The Efficacy Evaluable Dataset Establishes That EBP Gel Is Bioequivalent Because It Is At Least As Good As The Reference Drug For Inflammatory, Non-Inflammatory And Total Lesions.

Following OGD's determination that EBP Gel was not bioequivalent to the reference drug, Atrix reviewed the efficacy evaluable data submitted in ANDA 65-112.[34] When data from one subject (12140) is removed from the statistical analyses because it is a highly influential endpoint or outlier, EBP Gel is not inferior and possibly better than Benzamycin. For inflammatory lesions and Global Assessment, the mean percent reduction in lesions remains within OGD's standard confidence limits, but the upper confidence limit is substantially higher for non-inflammatory lesions (0.826 – 2.167) and marginally higher for total lesions (0.872 – 1.309). While the confidence intervals are outside OGD's customary limits of 80 to 125%, that interval was determined based on standard pharmacokinetic crossover studies and not large, controlled parallel studies with clinical endpoints where there is greater patient variability. As noted by a consultant to FDA, the standard confidence limits by OGD are inappropriate for clinical endpoint studies.[35]

The tighter confidence limits, particularly the upper limit, may be appropriate for pharmacokinetic studies because product safety is typically related to drug concentrations in biological fluids. Accordingly, to rely on data establishing the safety of the innovator drug, it is reasonable that a generic should have similar drug concentrations. That is not

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34 ——————— Sc.D., "Atrix BEN0002: Strategy for Reanalysis and Results" (Oct. 25, 2003) (attached as Exhibit 6).

35 See 2003 Advisory Committee Transcript, *supra* note 28.

true or necessary for topical products where there is no measurable concentration of drug circulating systemically, and where the study population is sufficiently large enough to compare adverse effects based on actual results. A comparison of reported adverse events shows that there is no statistically significant difference between adverse events reported with EBP Gel and Benzamycin.[36] In the absence of safety concerns, determination that EBP Gel is not inferior to or at least as good as Benzamycin is sufficient to determine that a topical product for treatment of acne vulgaris is bioequivalent. This conclusion is consistent with OGD's approval of a generic form of Permethrin Lotion 1%, a topical product used for treatment of lice, in which the reviewer noted "[b]ioequivalence is demonstrated when the imitator product is shown to be not inferior to the reference drug product."[37]

In short, reanalysis of the efficacy evaluable dataset with the exclusion of one highly influential data point, indicates that EBP Gel, like Permethrin, is "not inferior to" or at least as good as the reference drug, and possibly better. Consistent with OGD precedent, ANDA 65-112 should be approved.

D. Approval Of The EBP Gel Is Consistent With Agency Precedent And With FDA's Discretion To Determine How Bioequivalence Is To Be Determined

FDA's refusal to approve EBP Gel is inconsistent with agency precedents. FDA has approved ANDAs and NDAs for similar products (either by indication or dosage form) based on data different from or less than what FDA is now claiming in the not approvable letter is required for approval of EBP Gel.[38]

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36 See Memorandum from [redacted] to Steven Garrett, at 1 (Nov. 3, 2003) (attached as Exhibit 7).

37 Permethrin Crème Rinse 1%, ANDA 75-014, Medical Officer Review, Memorandum from Phyllis A. Heune, M.D., Medical Officer, Division of Dematologic and Dental Drug Products, to Linda Katz, M.D., Division of OTC Drugs, at 3 (June 24, 1999).

38 See Exhibit 8, which is a summary of some of the agency precedents for products used for treatment of acne vulgaris and topical products used for other conditions where the SBA, medical officer, or statistical reviews are readily available.

FDA has approved at least one ANDA for a similar gel product to treat acne vulgaris without a clinical study. In 1997, FDA granted a waiver of in vivo bioequivalence for erythromycin topical gel USP 2% pursuant to 21 C.F.R. § 320.22(b)(3).[39] EBP Gel, like the erythromycin gel, met the requirement that the product be a "solution for application to the skin, . . . tincture, or . . . similar other solubilized form."[40] FDA's statement in its letter denying Atrix's waiver request that 21 C.F.R. § 320.22(b)(3) "is not applicable to this dosage form" is inconsistent with FDA's action with respect to erythromycin gel.[41]

Contrary to FDA's assertions in the non approval letter, review of FDA's approval of similar products shows that FDA does not require proof of superiority to vehicle for all three lesion counts (inflammatory, non-inflammatory, and total).[42] FDA has stated repeatedly in the context of medical officer and statistical reviews that acne vulgaris products are only required to be effective for two out of three of the lesion counts (inflammatory, non-inflammatory, and total).[43] By this standard, both EBP Gel

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39 Erythromycin Topical Gel USP 2%, ANDA 64-184, Review of Waiver Request of Bioequivalence Study Requirement for a Topical Gel (Jan. 17, 1997).

40 21 C.F.R. § 320.22(b)(3) (emphasis added).

41 FDA May 8, 2000 letter, *supra* note 2, at 1.

42 Tables in the prescribing information for Benzamycin Pak, a line extension of the reference product, state that Benzamycin Pak was not superior to Benzamycin Pak vehicle for non-inflammatory lesions in one of the two studies conducted. Other examples include the ANDAs for Permethrin Lotion 1% for treatment of head lice and Permethrin Cream 5% for treatment of scabies for which the clinical studies supporting bioequivalence did not even include a vehicle in order to determine superiority.

43 See, e.g., Benzaclin Topical Gel, NDA 50-756, Statistical Review, at 3 (Nov. 17, 1998) (stating that "[s]tatistically significant difference in two of three lesion count parameters (Inflammatory, Non-Inflammatory and total lesion count) is acceptable by the agency"); Estrostep Tablets, NDA 21-276/6S, Statistical Review and Evaluation, at 3 (undated) (stating that "[a] prima facie case for a claim of efficacy is established when the sponsor achieves statistically significant differences in favor of treatment in two of the three lesion counts, AND in the dichotomized Facial Global Assessment"); Tazorac Cream 0.1%, NDA 21-184,

(continued . . .)

and Benzamycin would be approved. Moreover, FDA's statement in the not approvable letter that it "will not approve drug products for [acne vulgaris] without the applicant/sponsor having to demonstrate effectiveness for both inflammatory and non-inflammatory lesions" is inconsistent with the action FDA has taken.[44] Specifically, the SBA and the statistical and medical officer reviews for the reference drug product establish that Benzamycin was approved based on effectiveness data for inflammatory lesions alone. Other examples are described in Exhibit 8. If FDA were to require Atrix to be superior to vehicle on all three measures, FDA would be requiring a much more onerous showing for a generic product than it requires for reference products. And, in any event, proof of superiority over vehicle, as with the Permethrin products, should not be required to establish bioequivalency to a reference drug already determined to be effective.

It should also be noted that FDA has approved at least one topical ANDA for an acne treatment product for which the 80 to 125% confidence interval was not met. FDA approved an ANDA for clindamycin phosphate topical gel USP 1% for the treatment of acne vulgaris despite the fact that the 90% confidence interval for percent change from baseline for non-inflammatory lesions was not within the 80 to 125% range. In fact, the range was 69 to 114% for the modified intent to treat population and 64 to 108% for the per protocol population. In that case, the product failed to meet the lower limit of the confidence interval for non-inflammatory lesions, which suggests that the test product is less effective than the reference product. The statistical reviewer noted that if FDA "compare[d] the confidence limits for the ratio with the usual 'goalposts' of 80% to 125% used in blood-level BE studies, we would have a problem with [the non-inflammatory lesions], but the [inflammatory and total lesions] would pass. Of course, 'goalposts' other than 80% to 125% may be appropriate for clinical outcomes such as this."[45] This

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(continued . . .)

Statistical Review and Evaluation, at 3 (undated) (stating that "[t]he Division's recommendation for establishing efficacy in acne trials is to demonstrate (i) statistical significance for active versus vehicle in reducing lesions for two out of three types of lesions (inflammatory, non-inflammatory, and total lesions), and (ii) statistical significance in the 'success rate' for the overall acne assessment").

44 FDA Aug. 26, 2003 letter, *supra* note 16, at 2.

45 Clindamycin Phosphate Gel USP 1%, ANDA 64-160, Statistical Review, at 7 (Jan. 19, 2000).

statement demonstrates FDA's recognition of the need for exercising its discretion in determining whether a test product is bioequivalent to the reference product, particularly in the context of clinical endpoints.

Even without removal of a single outlier from the EBP Gel data, the data presented in ANDA 65-112 fall within the clindamycin phosphate gel precedent. Both EBP Gel and clindamycin phosphate gel were within the standard confidence interval for inflammatory lesions. Although the confidence interval is wider for the comparison of EBP Gel to the reference drug than existed for the generic clindamycin phosphate gel, the differences are due primarily to the EBP Gel being above the upper limit of 125%. This suggests EBP Gel may be more effective than the reference, not less, as is the case for clindamycin phosphate gel. When the dataset is reanalyzed, as discussed in section II.C above, it is even clearer that the EBP Gel ANDA should be approved because EBP Gel is within the lower end of the bioequivalence confidence interval on all three measures and exceeds the upper end of the confidence interval for non-inflammatory and total lesions only, which indicates that EBP Gel is no worse than and probably slightly more effective than the reference product.

Finally, FDA has approved an ANDA for another topical product – Permethrin Lotion 1% for the treatment of head lice – even though the 90% confidence interval for the pre-specified primary endpoint of "Treatment Success" did not fall within the usual allowable limits of 80 to 125% for either the intent to treat population or the efficacy valid population because the generic was more effective than the reference drug. In that case, the sponsor proposed in the final study report an additional primary endpoint of "Treatment Cure" for which the 90% confidence interval did fall within the usual allowable limits. The OGD Medical Officer Review questioned whether this primary endpoint was appropriate and asked for a consult from the relevant CDER new drug division. The Division of Dermatologic and Dental Drug Products review stated that "[i]t is felt that the primary efficacy endpoint should be Treatment Success . . . Bioequivalence is demonstrated when the [imitator] product is shown to be not inferior to the reference drug product. This means that the [imitator] product may be superior to the reference product."[46]

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[46] Permethrin Crème Rinse 1%, ANDA 75-014, *supra* note 37, at 3. The Medical Officer's superior noted on the review that "while [he did] not accept that noninferiority demonstrates bioequivalence, [he] concur[s] that bioequivalence has been demonstrated for the efficacy signal for these two products." Id.

This situation is nearly identical to the situation with EBP Gel. Even if FDA requires evaluation of the endpoints regarded by Atrix as secondary endpoints for approval of the ANDA, this precedent illustrates that FDA should approve the EBP Gel ANDA because EBP Gel, like Permethrin Lotion 1%, is no worse than and possibly more effective than the reference product. Moreover, this ANDA was approved without a vehicle control or any showing that either the reference product or generic product was statistically significantly superior to vehicle.

These examples demonstrate that FDA has approved products with data and study designs different from, and in some cases less than, what it is now requiring for Atrix. Given the discretion that FDA has in determining bioequivalence, in accordance with these precedents, FDA can and should approve the EBP Gel ANDA.

III. Conclusion and Expected Outcome

ANDA 65-112 should be approved. Approval would be consistent with Congress's intent to speed and simplify the approval of low cost generic drugs that benefit consumers and public health. It is an intent endorsed by every Commissioner of FDA including the current Commissioner. Approval would be consistent with widespread agency precedent and the discretion granted to FDA to determine bioequivalence. Approval should be granted because EBP Gel is bioequivalent to the reference drug and within FDA's standard bioequivalence confidence limits based on analyses of the primary endpoints set forth in the study protocol and relied on by FDA for the approval of the reference drug. Approval would be consistent with a determination that EBP Gel is at least as good as and possibly better than the reference drug at treating non-inflammatory lesions and total lesions. Conversely, failure to approve ANDA 65-112 would hold EBP Gel to standards not required by law, new drugs, precedent or science.

After your review of this letter, we request the opportunity to meet and to address any unresolved issues. The primary contact will be Roger Thies at Hyman, Phelps & McNamara, P.C. who can be reached by telephone at (202) 737-4285 and by fax at (202) 737-9329.

Sincerely,

Roger C. Thies /mjb

Hyman, Phelps & McNamara, P.C.

Attachments

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NEW CORRESP
NC 2/25/04

November 5, 2003

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 65-112 Erythormycin-Benzoyl Peroxide Topical Gel USP, 3%/5%

Dear Mr. Buehler:

Attached please find the Formal Dispute Resolution Request for the above-referenced ANDA. This document was forwarded to Mr. Buehler, Director, OGD yesterday by our legal representatives, Hyman, Phelps & McNamara.

Please file this copy to the ANDA. If you have any questions, please feel free to contact me at: 970-212-4901.

Sincerely,

ATRIX LABORATORIES, INC.

Cheri Jones

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

RECEIVED
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DIRECT DIAL (202) 737-4285

December 2, 2003

BY FEDERAL EXPRESS

Mr. Gary J. Buehler
Director
Office of Generic Drugs
Food and Drug Administration (HFD-600)
Center for Drug Evaluation and Research
7500 Standish Place, Room 286
Rockville, Maryland 20855

Re: Formal Dispute Resolution Request
Abbreviated New Drug Application 65-112
Erythromycin – Benzoyl Peroxide Topical Gel UPS, 3%/5%

Dear Mr. Buehler:

On November 4, 2003, Hyman, Phelps & McNamara, P.C. submitted a request for formal dispute resolution on behalf of Atrix Laboratories, Inc. ("Atrix") that requested that the Office of Generic Drugs approve ANDA 65-112.

Attached is an opinion from ——— M.D., Emeritus Professor of Dermatology, University of ——— that supports the approval of the Atrix generic erythromycin – benzoyl peroxide topical gel ("EBP Gel") for treatment of acne vulgaris.

In his opinion, Dr. ——— points out that FDA has not required that a drug be demonstrated to be effective for inflammatory, non-inflammatory and total lesions in order

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to be approved for treatment of acne vulgaris. Significant reduction in two out of three lesion categories plus significant global improvement has been sufficient for approval. Thus, Atrix's EBP Gel meets FDA's standards for effectiveness contrary to the assertion in FDA's letter to Atrix dated August 26, 2003.

Further, Dr. ——— states that there is no medically meaningful difference in safety between EBP Gel and the reference drug. Exceeding the upper confidence limit of 125%, which is typically applied by the agency for systemic drugs for safety reasons, is not applicable for topical agents that do not have greater cutaneous toxicity associated with greater levels of efficacy.

We request that Dr. ——— 's opinion be added to and incorporated in Atrix's request for formal dispute resolution and approval of ANDA 65-112. I have requested that Atrix submit a copy of this letter to ANDA 65-112.

Sincerely,

Roger C. Thies

Roger C. Thies

RCT/map
Attachment

cc: Steve Garrett

[redacted]

[redacted] M.D.
Professor of Dermatology

Department of Dermatology

November 24, 2003

Mr. Roger Thies
Hyman, Phelps & McNamara, PC
700 13th Street N.W.
Suite 1200
Washington, DC 20005

Tel: 202-737-4285
Fax: 202-737-9329

Dear Mr. Thies,

I have reviewed the data from the clinical trial comparing Benzamycin, the Atrix generic formulation and its vehicle. The study consisted of 360 patients randomized into three areas in a 2:2:1 ratio who were treated for 12 weeks. It is of interest that this design far exceeded the pivotal trials for Benzamycin which were done in two groups of patients (120 and 84) who were treated with two different formulations. Benzamycin approval was based on percent reduction of inflammatory lesions.

In the clinical trial comparing Benzamycin and the Atrix formulation and its vehicle, both active products produced a significant reduction in total lesions, inflammatory lesions and global assessment compared to the vehicle. No significant difference was found between the two agents and the vehicle for non-inflammatory lesions. Both Benzamycin and the Atrix formulation did produce a greater mean percent reduction, and mean reduction of non-inflammatory lesions from baseline. These data are not surprising in view of the well known minimal effect of antimicrobial agents on the non-inflammatory phase of acne pathophysiology. The main effects of antimicrobial agents are in the bacterium P. acnes which generates pro-inflammatory stimuli. This class of agent primarily reduces inflammatory lesions and produces a modest reduction in non-inflammatory agents. These two effects result in a reduction of total number of lesions. The Global Assessment method was different than that used today for new agents but was state of the art then and similar to that used for the original Benzamycin studies.

I very much disagree with the FDA Reviewer who says that an effective agent must produce a significant reduction of all types of lesions, i.e. non-inflammatory, inflammatory and total lesions as well as global improvement. The current standards for a new drug approval in acne are that the active agent must produce significant reduction in 2 of 3 (Total, inflammatory, non-inflammatory) plus significant global improvement when compared to the vehicle or placebo for

systemic agents. The reviewer is demanding greater efficacy for approval of a generic than for a new drug. Benzamycin would not have met criteria for approval had the FDA relied on reduction of non-inflammatory, inflammatory and total lesions because Benzamycin was not more effective than its individual ingredients in reducing non-inflammatory lesions. Is Benzamycin to be removed from the market place in spite of a long, well accepted usefulness in treating patients with moderate inflammatory acne?

The currently used measurements of bioequivalence are that the 90% confidence limits for the generic formulation should fall within 80% to 125% levels for the reference drug. It is generally recognized that these endpoints are fuzzier than plasma. These limits were met for % reduction in inflammatory lesions and global assessment. In the case of total lesions and non-inflammatory lesions (when one extreme outlier was removed) the 80% lower limit was met but the 125% upper limit was exceeded. Unlike systemic agents where higher plasma levels can be associated with significant toxicities for some drugs, topical agents do not have greater cutaneous toxicity associated with greater levels of efficacy.

The adverse events described for Benzamycin and the Atrix formulation are typical for topical anti-acne formulations. In my judgment, there is no medically meaningful difference in safety between the reference Atrix products.

In sum, my analysis of the data is that the Atrix formulation is equivalent to Benzamycin in terms of % reduction of inflammatory lesions, total lesions and global assessment and that both agents are significantly superior to the vehicle. In my opinion these data are sufficient to approve the Atrix erythromycin-benzoyl peroxide topical gel for treatment of acne.

Sincerely,

Emeritus Professor of Dermatology
University of

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*NOT ADMITTED IN DC

January 20, 2004

HAND DELIVER

Mr. Gary J. Buehler
Director
Office of Generic Drugs
Food and Drug Administration (HFD-600)
Center for Drug Evaluation and Research
7500 Standish Place, Room 286
Rockville, Maryland 20855

Re: Formal Dispute Resolution Request
Abbreviated New Drug Application 65-112
Erythromycin – Benzoyl Peroxide Topical Gel UPS, 3%/5%

Dear Mr. Beuhler:

On November 4, 2003, Atrix Laboratories, Inc. ("Atrix") submitted the above-captioned appeal. As of this date, there has been no substantive resolution. Based on conversations with Ms. Rita Hassall, who has been most responsive, it is my understanding that the Office of Generic Drugs ("OGD") is consulting with the Division of Dermatologic and Dental Drug Products ("DDDDP") prior to completing OGD's review.

We understand that because ANDAs are not subject to PDUFA, the Agency's commitment to respond to appeals within 30 days is not applicable. We are also mindful of the difficulty of coordinating a consult with DDDDP, particularly during the holiday

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season. Nonetheless, section 562 of the Federal Food, Drug, and Cosmetic Act (FDC Act) states that a review "shall take place in a timely manner." FDA's guidance for formal dispute resolution states that for non-PDUFA products, all reasonable efforts should be made to complete the review "as expeditiously as possible." See "Guidance for Industry, Formal Dispute Resolution: Appeals Above the Division Level," at 7 (Feb. 2000). Presumably to meet the statutory standard of "timely manner," this same guidance provides for a 30-day review for PDUFA products. Id. at 6. Section 562 of the FDC Act does not, however, differentiate between PDUFA and non-PDUFA products. More than 75 days have passed since Atrix's formal dispute resolution request was filed.

Atrix requests that OGD take all necessary steps to encourage and complete its consult with DDDDP if that consult is needed to resolve the dispute. To that end, I have included an opinion from Dr. ———— that the Atrix product is bioequivalent to the reference drug. Dr.——— is well known to the medical reviewers in DDDDP, and he conducted the pivotal clinical trial that led to the approval of the reference drug.

Atrix is understandably anxious that the review process be completed and that the Atrix product be approved. If it would be helpful to you, we can submit opinions from other noted dermatologists to support that approval.

Sincerely,

Roger C. Thies

Roger C. Thies

RCT/map

Enclosure

cc: Rita Hassall, Associate Director
Steven Garrett, Vice President, Clinical Research

Department of Dermatology

January 6, 2004

Mr. Roger C. Thies
Hyman, Phelps & McNamara, P.C.
700 Thirteenth Street, N.W.
Suite 1200
Washington, DC 20008-5929

Dear Mr. Thies:

Thank you for the opportunity to review copies of the summary of the study report comparing the Atrix formulation of benzoyl peroxide-erythromycin with the reference drug Benzamycin and vehicle. After reviewing this material it is my considered opinion that the Atrix formulation fulfills the criteria for a generic equivalent of Benzamycin.

It should be noted that the clinical trials with the Atrix formulation showed a larger difference then one might normally expect with regard to the improvement of non inflammatory lesions. It should be noted, however, that benzoyl peroxide-erythromycin is not considered a primary treatment for the non-inflammatory lesions of acne. Rather, because of its antibacterial and anti-inflammatory properties, it is a primary treatment for inflammatory acne. Therefore any difference in the effect on non inflammatory lesions would not be relevant to the clinical application of the drug.

Finally it is important to note that comedones (non-inflammatory lesions) are notoriously difficult to count accurately. While there is reasonable correlation between the comedo counts of an individual investigator, there is wide variation in the counts between investigators. I would, therefore, place considerably less emphasis on the non-inflammatory lesion counts then on the inflammatory lesion counts, particularly in a drug which is not primarily intended for this purpose.

In summary, the Atrix formulation of benzoyl peroxide-erythromycin is, in my opinion, generically equivalent to the reference drug (Benzamycin) and the clinical data meet the two out of three standards previously required by the Food & Drug Administration.

If I can be of any further assistance, please do not hesitate to contact me.

Sincerely yours,

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February 23, 2004

ORIG AMENDMEN.

N/AC

Gary Buehler, Director
Office of Generic Drugs
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Metro Park North II
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Rockville, MD 20855

Re: ANDA 65-112
Erythromycin-Benzoyl Peroxide Topical Gel USP, 3%/5%
MINOR AMENDMENT

Dear Mr. Buehler:

Atrix Laboratories, Inc. is submitting a Minor Amendment to ANDA 65-112 seeking approval for the above-captioned product.

A response to the Agency's August 26, 2003 non-approvable letter based upon bioequivalence to the reference listed drug (RLD) was submitted as a Formal Dispute Resolution Request on November 5, 2003.

We are, at this time, seeking to reopen the ANDA based upon communication with the Agency.

If you have any questions, please feel free to contact me at: 970-212-4901.

Sincerely,

ATRIX LABORATORIES, INC.

Cheri Jones

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

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FEB 2 4 2004
OGD/G

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 01, 2004

NC mailed 3/15/04

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

Re: ANDA 65-112
Erythromycin-Benzoyl Peroxide Topical Gel USP, 3%/5%
LABELING COMMITMENT

Dear Mr. Buehler:

Atrix Laboratories, Inc. is submitting a Labeling Commitment to ANDA 65-112 for the above-captioned product as requested in a telephone conversation today with Michelle Dillahunt, FDA.

FDA has requested that Atrix update, at next printing, the "prior to reconstitution" statement of the storage condition temperature on the product insert. The change is from;

Prior to reconstitution, store at room temperature between 15° and 30°C (59° - 86°F)
to
Prior to reconstitution, store at 20° to 25°C (68° - 77°F). See USP Controlled Room Temperature.

Atrix commits to implement this change at next printing.

If you have any further questions, please feel free to contact me at: 970-212-4901 or by email at cjones@atrixlabs.com.

Sincerely,

ATRIX LABORATORIES, INC.

Lynn C Hansen for

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

3.1

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March 15, 2004

ORIG AMENDMENT
N/AC

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

Re: ANDA 65-112
Erythromycin-Benzoyl Peroxide Topical Gel USP, 3%/5%
CMC - MINOR AMENDMENT

Dear Mr. Buehler:

Atrix Laboratories, Inc. is submitting a Minor Amendment to ANDA 65-112 seeking approval for the above-captioned product. This minor amendment is in response to a request from the chemistry reviewer on March 15, 2004 for updated stability data on the bio/exhibit batch.

Full data is available for the 24-month test station at this time and Atrix is requesting a 24 month expiration dating for the product. Stability Summary Reports and a summary discussion on the Erythromycin data are attached. There have been three (3) significant observations made during the course of the stability program concerning the Erythromycin potency determinations.

[Stability data for the bio/exhibit batch, 1304 and1304A, has completed 36-month testing interval for immediate use (IU). Delayed use (DU) 36-month data will be completed later this month.]

Additionally, Atrix has incorporated Agency comments for other ANDA CMC amendments during the past year into the documentation for this product. The following changes to the Finished Product, Regulatory Shelf-Life specifications and Stability Protocol are being updated at this time:

MAR 16 2004

- [redacted]
- Documents have been updated to reference USP/NF compendial testing where appropriate.

[redacted]

If you have any further requests or questions, please feel free to contact me at: 970-212-4901 or cjones@atrixlabs.com.

Sincerely,

ATRIX LABORATORIES, INC.

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

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March 16, 2004

ORIG AMENDMENT
N/AC

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

Re: ANDA 65-112
Erythromycin-Benzoyl Peroxide Topical Gel USP, 3%/5%
CMC - MINOR AMENDMENT

Dear Mr. Buehler:

Atrix Laboratories, Inc. is submitting a Minor Amendment to ANDA 65-112 seeking approval for the above-captioned product. This minor amendment is in response to a request from the chemistry reviewer.

The Regulatory Finished Product and Stability Specifications and the Stability Protocol have been updated with the following corrections;

[redacted] ;

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MAR 18 2004
OGD/CDER

If you have any further requests or questions, please feel free to contact me at: 970-212-4901 or cjones@atrixlabs.com.

Sincerely,

ATRIX LABORATORIES, INC.

Cheri Jones

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