CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 75-006

Name:	Chlorhexidine Gluconate Oral Rinse USP, 0.12%
Sponsor:	Morton Grove Pharmaceuticals, Inc.
Approval Date:	March 3, 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-006

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Reviews / Information Included in this Review	
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Statistical Review(s)	
Microbiology Review(s)	
Administrative Document(s)	X
Correspondence	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-006

APPROVAL LETTER

ANDA 75-006

MAR 3 2004

Morton Grove Pharmaceuticals, Inc.
Attention: Sheeja T. George
6451 West Main Street
Morton Grove, IL 60053

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated November 15, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Chlorhexidine Gluconate Oral Rinse USP, 0.12%.

Reference is also made to your amendments dated January 22, August 1, and December 11, 2003, and February 10, 2004.

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 Chlorhexidine Gluconate Oral Rinse USP, 0.12%, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Peridex® Oral Rinse of Zila Pharmaceuticals, Inc.).

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

cc: ANDA 75-006
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205
HFD-610/Orange Book Staff

Endorsements:
HFD-600/N.Nashed/ 3/1/04
HFD-623/J.Fan/ 2/27/04
HFD-617/T.Vu/ 3/1/04
HFD-613/~~L.Golson~~/B. Weltzman 3/1/2004
HFD-613/J.Grace/ 3/1/2004

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F/T by

APPROVAL

Robert West
3/3/2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-006

APPROVED LABELING

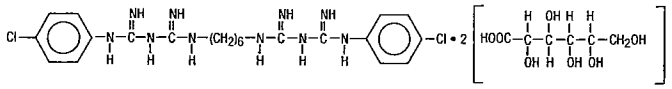
CHLORHEXIDINE GLUCONATE ORAL RINSE 0.12%

APPROVAL

MAR 03 2004

DESCRIPTION

Chlorhexidine gluconate oral rinse is an oral rinse containing 0.12% chlorhexidine gluconate (1,1'-hexamethylene bis [5-(p-chlorophenyl) biguanide] di-D-gluconate) in a base containing water, 11.6% alcohol, glycerin, PEG-40 sorbitan diisostearate, peppermint stick flavor, sodium saccharin, and FD&C Blue No. 1. Chlorhexidine gluconate oral rinse is a near-neutral solution (pH range 5-7). Chlorhexidine gluconate is a salt of chlorhexidine and gluconic acid. Its molecular formula is $C_{22}H_{30}Cl_2N_{10}\bullet 2C_6H_{12}O_7$, the molecular weight is 897.77 and it has the following structural formula:



CLINICAL PHARMACOLOGY

Chlorhexidine gluconate oral rinse provides microbicidal activity during oral rinsing. The clinical significance of chlorhexidine gluconate oral rinse's anti-microbial activities is not clear. Microbiological sampling of plaque has shown a general reduction of counts of certain assayed bacteria, both aerobic and anaerobic, ranging from 54-97% through six months' use.

Use of chlorhexidine gluconate oral rinse in a six-month clinical study did not result in any significant changes in bacterial resistance, overgrowth of potentially opportunistic organisms or other adverse changes in the oral microbial ecosystem. Three months after chlorhexidine gluconate use was discontinued, the number of bacteria in plaque had returned to baseline levels and resistance of plaque bacteria to chlorhexidine gluconate was equal to that at baseline.

Pharmacokinetics

Pharmacokinetic studies with a 0.12% chlorhexidine gluconate oral rinse indicate approximately 30% of the active ingredient, chlorhexidine gluconate, is retained in the oral cavity following rinsing. This retained drug is slowly released into the oral fluids. Studies conducted on human subjects and animals demonstrate chlorhexidine gluconate is poorly absorbed from the gastrointestinal tract. The mean plasma level of chlorhexidine gluconate reached a peak of 0.206 μg/g in humans 30 minutes after they ingested a 300 mg dose of the drug. Detectable levels of chlorhexidine gluconate were not present in the plasma of these subjects 12 hours after the compound was administered. Excretion of chlorhexidine gluconate occurred primarily through the feces (~90%). Less than 1% of the chlorhexidine gluconate ingested by these subjects was excreted in the urine.

INDICATIONS AND USAGE

Chlorhexidine gluconate oral rinse is indicated for use between dental visits as part of a professional program for the treatment of gingivitis as characterized by redness and swelling of the gingivae, including gingival bleeding upon probing. Chlorhexidine gluconate oral rinse has not been tested among patients with acute necrotizing ulcerative gingivitis (ANUG). For patients having coexisting gingivitis and periodontitis, see **PRECAUTIONS**.

CONTRAINDICATIONS

Chlorhexidine gluconate oral rinse should not be used by persons who are known to be hypersensitive to chlorhexidine gluconate.

WARNINGS

The effect of chlorhexidine gluconate oral rinse on periodontitis has not been determined. An increase in supragingival calculus was noted in clinical testing in chlorhexidine gluconate oral rinse users compared with control users. It is not known if chlorhexidine gluconate use results in an increase in subgingival calculus. Calculus deposits should be removed by a dental prophylaxis at intervals not greater than six months. Hypersensitivity and generalized allergic reactions have occurred. See **CONTRAINDICATIONS.**

PRECAUTIONS

General

1. For patients having coexisting gingivitis and periodontitis, the presence or absence of gingival inflammation following treatment with chlorhexidine gluconate oral rinse should not be used as a major indicator of underlying periodontitis.
2. Chlorhexidine gluconate oral rinse can cause staining of oral surfaces, such as tooth surfaces, restorations, and the dorsum of the tongue. Not all patients will experience a visually significant increase in toothstaining. In clinical testing, 56% of chlorhexidine gluconate oral rinse users exhibited a measurable increase in facial anterior stain, compared to 35% of control users after six months; 15% of chlorhexidine gluconate oral rinse users developed what was judged to be heavy stain, compared to 1% of control users after six months. Stain will be more pronounced in patients who have heavier accumulations of unremoved plaque.

   Stain resulting from use of chlorhexidine gluconate oral rinse does not adversely affect health of the gingivae or other oral tissues. Stain can be removed from most tooth surfaces by conventional professional prophylactic techniques. Additional time may be required to complete the prophylaxis.

   Discretion should be used when prescribing to patients with anterior facial restorations with rough surfaces or margins. If natural stain cannot be removed from these surfaces by a dental prophylaxis, patients should be excluded from chlorhexidine gluconate treatment if permanent discoloration is unacceptable. Stain in these areas may be difficult to remove by dental prophylaxis and on rare occasions may necessitate replacement of these restorations.
3. Some patients may experience an alteration in taste perception while undergoing treatment with chlorhexidine gluconate oral rinse. Rare instances of permanent taste alteration following chlorhexidine gluconate oral rinse use have been reported.

Pregnancy: Teratogenic Effects - Pregnancy Category B

Reproduction studies have been performed in rats and rabbits at chlorhexidine gluconate doses up to 300 mg/kg/day and 40 mg/kg/day, respectively, and have not revealed evidence of harm to the fetus. However, adequate and well-controlled studies in pregnant women have not been done. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when chlorhexidine gluconate is administered to a nursing woman.

In parturition and lactation studies with rats, no evidence of impaired parturition or of toxic effects to suckling pups was observed when chlorhexidine gluconate was administered to dams at doses up to 100 mg/kg/day.

Pediatric Use

Clinical effectiveness and safety of chlorhexidine gluconate oral rinse have not been established in pediatric patients under the age of 18.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a drinking water study in rats, carcinogenic effects were not observed in two mammalian *in vivo* mutagenesis studies with chlorhexidine gluconate. The highest

doses of chlorhexidine used in a mouse dominant-lethal assay and a hamster cytogenetics test were 1000 mg/kg/day and 250 mg/kg/day, respectively. No evidence of impaired fertility was observed in rats at doses up to 100 mg/kg/day.

ADVERSE REACTIONS

The most common side effects associated with chlorhexidine gluconate oral rinses are (1) an increase in staining of teeth and other oral surfaces, (2) an increase in calculus formation, and (3) an alteration in taste perception; see **WARNINGS** and **PRECAUTIONS**. Oral irritation and local allergy-type symptoms have been spontaneously reported as side effects associated with use of chlorhexidine gluconate rinse. The following oral mucosal side effects were reported during placebo-controlled adult clinical trials: aphthous ulcer, grossly obvious gingivitis, trauma, ulceration, erythema, desquamation, coated tongue, keratinization, geographic tongue, mucocele, and short frenum. Each occurred at a frequency of less than 1%.

Among postmarketing reports, the most frequently reported oral mucosal symptoms associated with chlorhexidine gluconate oral rinse are stomatitis, gingivitis, glossitis, ulcer, dry mouth, hypesthesia, glossal edema, and paresthesia.

Minor irritation and superficial desquamation of the oral mucosa have been noted in patients using chlorhexidine gluconate oral rinse.

There have been cases of parotid gland swelling and inflammation of the salivary glands (sialadenitis) reported in patients using chlorhexidine gluconate oral rinse.

OVERDOSAGE

Ingestion of 1 or 2 ounces of chlorhexidine gluconate oral rinse by a small child (~10 kg body weight) might result in gastric distress, including nausea, or signs of alcohol intoxication. Medical attention should be sought if more than 4 ounces of chlorhexidine gluconate oral rinse is ingested by a small child or if signs of alcohol intoxication develop.

DOSAGE AND ADMINISTRATION

Chlorhexidine gluconate oral rinse therapy should be initiated directly following a dental prophylaxis. Patients using chlorhexidine gluconate oral rinse should be reevaluated and given a thorough prophylaxis at intervals no longer than six months.

Recommended use is twice daily oral rinsing for 30 seconds, morning and evening after toothbrushing. Usual dosage is 1/2 fl oz (marked in cup) of undiluted product. Patients should be instructed to not rinse with water, or other mouthwashes, brush teeth, or eat immediately after using chlorhexidine gluconate oral rinse. Chlorhexidine gluconate oral rinse is not intended for ingestion and should be expectorated after rinsing.

HOW SUPPLIED

Chlorhexidine Gluconate Oral Rinse is supplied as a light blue liquid in 1 pint (473 mL) child-resistant bottles, individually cartoned with a dosage cup.

Store above freezing (32 °F or 0 °C).

Dispense in original container or in amber glass bottles.

Rx Only

Product No.: 8154

Manufactured By:
Morton Grove Pharmaceuticals, Inc.
Morton Grove, IL 60053

28154
ISS. 1-99

Morton Grove Pharmaceuticals, Inc.
Morton Grove, IL 60053

D5-006

CHLORHEXIDINE GLUCONATE ORAL RINSE 0.12%

1 PINT (473 mL) FINAL PRINTED LABEL

MGP

NDC 60432-154-16

CHLORHEXIDINE GLUCONATE ORAL RINSE 0.12%

DIRECTIONS FOR USE: Fill dosage cup to the ½ fl oz line. Swish in mouth undiluted for 30 seconds then spit. Use after breakfast and before bedtime. Or, use as prescribed.

NOTE: To minimize medicinal taste, do not rinse with water immediately after use.

INGREDIENTS: 0.12% chlorhexidine gluconate in a base containing water, 11.6% alcohol, glycerin, USP, PEG-40 sorbitan diisostearate, peppermint stick flavor, sodium saccharin, USP, and FD&C Blue No. 1.

KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

Store above freezing (32 °F or 0 °C).

Rx Only

NET: 1 Pint (473 mL)

WHAT TO EXPECT WHEN USING CHLORHEXIDINE GLUCONATE ORAL RINSE

Your dentist has prescribed chlorhexidine gluconate oral rinse to treat your gingivitis–to help reduce the redness and swelling of your gums, and also to help you control any gum bleeding. Use chlorhexidine gluconate oral rinse regularly, as directed by your dentist, in addition to daily brushing and flossing. Spit out after use, chlorhexidine gluconate oral rinse should not be swallowed.

Chlorhexidine gluconate oral rinse may cause some tooth discoloration, or increases in tartar (calculus) formation, particularly in areas where stain and tartar usually form. It is important to see your dentist for removal of any stain or tartar at least every six months, or more frequently if your dentist advises.

- Both stain and tartar can be removed by your dentist or hygienist. Chlorhexidine gluconate oral rinse may cause permanent discoloration of some front-tooth fillings.
- To minimize discoloration, you should brush and floss daily, emphasizing areas which begin to discolor.
- Local hypersensitivity and sometimes generalized allergic reactions have also been reported. Chlorhexidine gluconate oral rinse should not be used by persons who have a sensitivity to it or its components.

Chlorhexidine gluconate oral rinse may taste bitter to some patients and can affect how foods and beverages taste. This will become less noticeable in most cases with continued use of chlorhexidine gluconate oral rinse.

- To avoid taste interference, rinse with chlorhexidine gluconate oral rinse *after* meals. Do not rinse with water or other mouthwashes immediately after rinsing with chlorhexidine gluconate oral rinse.

If you have any questions or comments about chlorhexidine gluconate oral rinse, contact your dentist or pharmacist.

See accompanying package insert for prescribing information.

APPROVED MAR 03 2004

PLACE PHARMACY LABEL HERE

Dispense in original container or in amber glass.

Manufactured By:
Morton Grove Pharmaceuticals, Inc. 50-8154-16
Morton Grove, IL 60053 ISS. 6-98

N 3 60432-154-16 1

DIRECTIONS FOR USE:
Fill dosage cup to the ½ fl oz line. Swish in mouth undiluted for 30 seconds then spit. Use after breakfast and before bedtime. Or, use as prescribed.

NOTE: To minimize medicinal taste, do not rinse with water immediately after use.

KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

Manufactured By:
Morton Grove Pharmaceuticals, Inc.
Morton Grove, IL 60053

MGP

NDC 60432-154-16

CHLORHEXIDINE GLUCONATE ORAL RINSE 0.12%

APPROVAL

MAR 03 2004

Rx Only

NET: 1 Pint (473 mL)

CHLORHEXIDINE GLUCONATE ORAL RINSE

NDC 60432-154-16

INGREDIENTS: 0.12% chlorhexidine gluconate in a base containing water, 11.6% alcohol, glycerin, USP, PEG-40 sorbitan diisostearate, peppermint stick flavor, sodium saccharin, USP, and FD&C Blue No. 1.

See accompanying package insert for prescribing information.

Store above freezing (32 °F or 0 °C).

Dispense in original container or in amber glass.

See top flap of carton for lot number and expiration date.

Manufactured By:
Morton Grove
Pharmaceuticals, Inc.
Morton Grove, IL 60053

5-50-8154-16
ISS. 6-98

WHAT TO EXPECT WHEN USING CHLORHEXIDINE GLUCONATE ORAL RINSE

Your dentist has prescribed chlorhexidine gluconate oral rinse to treat your gingivitis–to help reduce the redness and swelling of your gums, and also to help you control any gum bleeding. Use chlorhexidine gluconate oral rinse regularly, as directed by your dentist, in addition to daily brushing and flossing. Spit out after use, chlorhexidine gluconate oral rinse should not be swallowed.

Chlorhexidine gluconate oral rinse may cause some tooth discoloration, or increases in tartar (calculus) formation, particularly in areas where stain and tartar usually form. It is important to see your dentist for removal of any stain or tartar at least every six months, or more frequently if your dentist advises.

- Both stain and tartar can be removed by your dentist or hygienist. Chlorhexidine gluconate oral rinse may cause permanent discoloration of some front-tooth fillings.
- To minimize discoloration, you should brush and floss daily, emphasizing areas which begin to discolor.
- Local hypersensitivity and sometimes generalized allergic reactions have also been reported. Chlorhexidine gluconate oral rinse should not be used by persons who have a sensitivity to it or its components.

Chlorhexidine gluconate oral rinse may taste bitter to some patients and can affect how foods and beverages taste. This will become less noticeable in most cases with continued use of chlorhexidine gluconate oral rinse.

- To avoid taste interference, rinse with chlorhexidine gluconate oral rinse *after* meals. Do not rinse with water or other mouthwashes immediately after rinsing with chlorhexidine gluconate oral rinse.

If you have any questions or comments about chlorhexidine gluconate oral rinse, contact your dentist or pharmacist.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-006

LABELING REVIEW(S)

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

ANDA Number: **75-006** Date of Submission: **November 12, 1997**

Applicant's Name: **Morton Grove Pharmaceuticals, Inc.**

Established Name: **Chlorhexidine Gluconate Oral Rinse**

Labeling Deficiencies:

1. CONTAINER (473 mL)

   a. Revise the DIRECTIONS FOR USE to read as follows:

      ...30 seconds then spit. Use after breakfast and before bedtime. Or...

   b. WHAT TO EXPECT WHEN USING CHLORHEXIDINE GLUCONATE ORAL RINSE

      i. Insert the following text as the last sentence of paragraph one:

         Spit out after use, chlorhexidine gluconate oral rinse should not be swallowed.

      ii. Revise paragraph two to read as follows:

         ...particularly in areas where stain and tartar usually form. It is important to see...

      iii. Revise the third bullet to read as follows:

         - Local hypersensitivity and sometimes generalized allergic...

      iv. Paragraph three - Delete the last sentence of this paragraph. [———————————...]

      v. Revise the fourth bullet to read as follows:

         - To avoid...water or other mouthwashes immediately after rinsing with chlorhexidine gluconate oral rinse.

c. We note the innovator has designated an area on the container label for the placement of the pharmacy label. You have not indicated that an area is reserved for this on your label. Please comment and/or revise.

2. CARTON (1 x 472 mL)

See comments a and b under CONTAINER.

3. INSERT

a. DESCRIPTION

Delete —— from the listing of inactive ingredients in 2 places.

b. CLINICAL PHARMACOLOGY

i. Paragraph one - Delete " ———— " from the last sentence of paragraph two.

ii. Pharmacokinetics

A). Revise the first sentence to read as follows:

...with a 0.12% chlorhexidine gluconate oral rinse indicate...active ingredient.

B). Delete the "hyphen" that appears between "300" and "mg".

c. WARNINGS

Revise to read as follows:

...It is not known if chlorhexidine gluconate use results in an...six months. Hypersensitivity and generalized allergic reactions have occurred. See CONTRAINDICATIONS.

d. PRECAUTIONS

i. General

A). Number 2, second paragraph - Stain resulting from use of...excluded from chlorhexidine gluconate treatment if permanent...Stain in these areas...

B). Number 3 - ...with chlorhexidine gluconate oral rinse. Rare instances of...rinse use have...

ii. Usage in Pregnancy - Revise this subsection heading to read "Pregnancy: Teratogenic Effects - Pregnancy Category B". In addition, revise the subsection to read as follows:

Reproduction studies have been performed in rats and rabbits at chlorhexidine gluconate doses up to 300 mg/day and 40 mg/kg/day, respectively, and have not revealed evidence of harm to the fetus. However, adequate and well-controlled studies in pregnant women have not been done. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

iii. Nursing Mothers - Revise to read as follows:

...exercised when chlorhexidine gluconate is administered...

In parturition...chlorhexidine gluconate was administered to dams at doses up to 100 mg/kg/day.

iv. Carcinogenesis, Mutagenesis - Revise this subsection heading to read "Carcinogenesis, Mutagenesis, Impairment of Fertility". In addition, revise the subsection to read as follows:

In a drinking water study in rats, carcinogenic effects were not observed in two mammalian *in vivo* mutagenesis studies with chlorhexidine gluconate. The highest doses of chlorhexidine used in a mouse dominant-lethal assay and a hamster cytogenetics test were 1000 mg/kg/day and 250 mg/kg/day, respectively. No evidence of impaired fertility was observed in rats at doses up to 100 mg/kg/day.

e. ADVERSE REACTIONS

i. Paragraph one, number 3 - Revise to read as follows:

...PRECAUTIONS. Oral irritation and local allergy-type symptoms have been spontaneously reported as side effects associated with use of chlorhexidine gluconate rinse. The following oral mucosal side effects were reported during placebo-controlled adult clinical trials: aphthous ulcer, grossly obvious gingivitis, trauma, ulceration, erythema, desquamation, coated tongue, keratinization, geographic tongue, mucocele, and short frenum. Each occurred at a frequency of less than 1%.

ii. Insert the following text to appear as the second paragraph:

Among postmarketing reports, the most frequently reported oral mucosal symptoms associated with chlorhexidine gluconate oral rinse are stomatitis, gingivitis, glossitis, ulcer, dry mouth, hypesthesia, glossal edema, and paresthesia.

iii. Revise paragraph two to read as follows:

Minor irritation...using chlorhexidine gluconate oral rinse.

iv. Revise the last paragraph to read as follows:

There have been cases of parotid gland swelling and inflammation of the salivary glands (sialadenitis) reported in patients using chlorhexidine gluconate oral rinse.

f. DOSAGE AND ADMINISTRATION

Chlorhexidine gluconate oral rinse therapy should be initiated...

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

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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.

John D. Bruce for/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes No

Container Labels:

Carton Labeling:

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Peridex Oral Rinse

NDA Number: 19-028

NDA Drug Name: Peridex Oral Rinse

NDA Firm: Procter and Gamble Company

Date of Approval of NDA Insert and supplement #: January 8, 1997/S-009
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: Approved container labels in file folder.
Basis of Approval for the Carton Labeling: Approved carton labeling in file folder.

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 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	

Labeling (continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		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 bioeqivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		X	

******NOTES/QUESTIONS TO THE CHEMIST:******

1. **Does the dosage cup provided deliver the labeled amount? I couldn't find any data on the cup at all. I wanted to be assured the cup will be packaged with the bottle and if it is clearly market ½ oz.**

FOR THE RECORD:

1. Review based on the labeling of the listed drug(Peridex Oral Rinse; 19-028/S-009; Approved January 8, 1997, Revised December 1996).

2. Patent/ Exclusivities:

   There are no patents or exclusivities that pertain to this drug product.

3. Storage/Dispensing Conditions:

   NDA: Store above freezing (32°F or 0°C). Dispense in bottle as provided or in amber glass.

   ANDA: Store above freezing (32°F or 0°C). Dispense in original container or in amber glass bottles.

   USP: Not a monograph in the USP of PF.

4. Product Line:

   The innovator markets their product in bottles containing 473 mL in cartons of 3.

   The applicant proposes to market their product in bottles containing 473 mL in cartons of 1.

5. Inactive Ingredients:

   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on pages 60 and 61, Vol. 2.1.

6. All manufacturing will be performed by Morton Grove Pharmaceuticals, Inc.. All outside firms are utilized for testing. See pages 202 and 593, Vol. 2.1.

7. Container/Closure:

   This product will be packaged in 16 oz **Amber** Round Bottle with a CRC closure.

8. The firm originally submitted this application in January with a different formulation. A refuse to file letter was sent because this product was classified as a topical and therefore had to have the same ingredients.

Date of Review: December 3, 1997

Date of Submission: November 12, 1997

Reviewer: Carol A. Holquist **Date:** 2/10/98

Team Leader: John Grace **Date:** 2/11/98

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cc:

ANDA 75-006
DUP/DIVISION FILE
HFD-613/CHolquist/JGrace (no cc)
12/3/97/X:\NEW\FIRMSAM\MORTON\LTRS&REV\75006NA1.L
Review

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

ANDA Number: 75-006 Date of Submission: July 10, 1998

Applicant's Name: Morton Grove Pharmaceuticals, Inc.

Established Name: Chlorhexidine Gluconate Oral Rinse, 0.12%

Labeling Deficiencies:

1. CONTAINER (473 mL)

   Satisfactory

2. CARTON (1 x 473 mL)

   Satisfactory

3. INSERT

   a. PRECAUTIONS

      i. General

         A) Revise to delete the second sentence, "[redacted]..." from Number 3.

         B) Revise the ultimate sentence of Number 3 to read, ...alteration following chlorhexidine...

      ii. Pregnancy

         Revise the first sentence to read, "...300 mg/kg/day..." (add "kg")

   b. DOSAGE AND ADMINISTRATION

      Revise so that the following becomes the third sentence of the second paragraph:

      Patients should be instructed to not rinse with water, or other mouthwashes, brush teeth, or eat immediately after using chlorhexidine gluconate oral rinse.

Please revise your package insert labeling, as instructed above, and submit in final print.

Please note that the Agency reserves the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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.

John D. Grace for

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes No

Container Labels: (473 mL)
Satisfactory as of July 10, 1998, submission

Carton Labeling: (1 x 473 mL)
Satisfactory as of July 10, 1998, submission

Professional Package Insert Labeling:

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Peridex Oral Rinse

NDA Number: 19-028

NDA Drug Name: Peridex Oral Rinse

NDA Firm: Procter and Gamble Company

Date of Approval of NDA Insert and supplement #: January 8, 1997/S-009
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: Approved container labels in file folder.
Basis of Approval for the Carton Labeling: Approved carton labeling in file folder.

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 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	

Labeling (continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		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 bioeqivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.		X	

******NOTES/QUESTIONS TO THE CHEMIST:******

1. **Does the dosage cup provided deliver the labeled amount? I couldn't find any data on the cup at all. I wanted to be assured the cup will be packaged with the bottle and if it is clearly market ½ oz.**

FOR THE RECORD:

1. Review based on the labeling of the listed drug(Peridex Oral Rinse; 19-028/S-009; Approved January 8, 1997, Revised December 1996).

2. Patent/ Exclusivities:

   There are no patents or exclusivities that pertain to this drug product.

3. Storage/Dispensing Conditions:

   NDA: Store above freezing (32°F or 0°C). Dispense in bottle as provided or in amber glass.

   ANDA: Store above freezing (32°F or 0°C). Dispense in original container or in amber glass bottles.

   USP: Not a monograph in the USP of PF.

4. Product Line:

   The innovator markets their product in bottles containing 473 mL in cartons of 3.

   The applicant proposes to market their product in bottles containing 473 mL in cartons of 1.

5. Inactive Ingredients:

   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on pages 60 and 61, Vol. 2.1.

6. All manufacturing will be performed by Morton Grove Pharmaceuticals, Inc.. All outside firms are utilized for testing. See pages 202 and 593, Vol. 2.1.

7. Container/Closure:

   This product will be packaged in 16 oz **Amber** Round Bottle with a CRC closure.

8. The firm originally submitted this application in January with a different formulation. A refuse to file letter was sent because this product was classified as a topical and therefore had to have the same ingredients.

Date of Review:
December 10, 1998

Date of Submission:
July 10, 1998

Primary Reviewer:

Date:
12/10/98

Team Leader:

Date:
12/10/98

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cc:

ANDA: 75-006
DUP/DIVISION FILE
HFD-613/LGolson/JGrace (no cc)
ldg/12/10/98/X:\NEW\FIRMSAM\MORTON\LTRS&REV\75006NA2.L
Review

APPROVAL SUMMARY

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

ANDA Number: 75-006 Date of Submission: February 9, 1999 and July 10, 1998 (Amendments)

Applicant's Name: Morton Grove Pharmaceuticals, Inc.

Established Name: Chlorhexidine Gluconate Oral Rinse, 0.12%

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: (473 mL)
Satisfactory as of July 10, 1998, submission

Carton Labeling: (1 x 473 mL)
Satisfactory as of July 10, 1998, submission

Professional Package Insert Labeling:
Satisfactory as of February 9, 1999, submission

Revisions needed post-approval:

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Peridex Oral Rinse

NDA Number: 19-028

NDA Drug Name: Chlorhexidine Gluconate Oral Rinse

NDA Firm: Procter & Gamble Company

Date of Approval of NDA Insert and supplements #007, 008, 009: January 8, 1997

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Side-by-side comparison

Basis of Approval for the Carton Labeling: Side-by-side comparison

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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 23		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	

Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling (continued)	Yes	No	N A
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			X
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		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 bioeqivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	

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

******NOTES/QUESTIONS TO THE CHEMIST:******

Does the dosage cup provided deliver the labeled amount? I couldn't find any data on the cup at all. I wanted to be assured the cup will be packaged with the bottle and if it is clearly market ½ oz. (YES. See Response in Feb. 9, 1999 submission)

FOR THE RECORD:

1. Review based on the labeling of the listed drug(Peridex Oral Rinse; 19-028/S-009; Approved January 8, 1997, Revised December 1996).

2. Patent/ Exclusivities:

   There are no patents or exclusivities that pertain to this drug product.

3. Storage/Dispensing Conditions:

   NDA: Store above freezing (32°F or 0°C). Dispense in bottle as provided or in amber glass.

   ANDA: Store above freezing (32°F or 0°C). Dispense in original container or in amber glass bottles.

   USP: Not a monograph in the USP of PF.

4. Product Line:

   The innovator markets their product in bottles containing 473 mL in cartons of 3.

   The applicant proposes to market their product in bottles containing 473 mL in cartons of 1.

5. Inactive Ingredients:

   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on pages 60 and 61, Vol. 2.1.

6. All manufacturing will be performed by Morton Grove Pharmaceuticals, Inc.. All outside firms are utilized for testing. See pages 202 and 593, Vol. 2.1.

7. Container/Closure:

   This product will be packaged in 16 oz **Amber** Round Bottle with a CRC closure.

8. The firm originally submitted this application in January with a different formulation. A refuse to file letter was sent because this product was classified as a topical and therefore had to have the same ingredients.

Date of Review:
March 4, 1999

Date of Submission:
February 9, 1999 and July 10, 1998 (Amendments)

Primary Reviewer:
L N O Golson

Date:
3/4/99

Team Leader:
John Grace

Date:
3/5/1999

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cc:

ANDA: 75-006
DUP/DIVISION FILE
HFD-613/LGolson/JGrace (no cc)
X:\NEW\FIRMSAM\MORTON\LTRS&REV\75006AP.L
Review

Concur: Christine Lopez 3/5/99

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-006

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 1

2. ANDA # 75-006

3. NAME AND ADDRESS OF APPLICANT

Morton Grove Pharmaceutical, Inc.
6451 West Main Street
Morton Grove, IL 60053

4. LEGAL BASIS FOR SUBMISSION

The firm knows of no patents that claim the reference listed drug product. Also believes that the reference listed drug is not entitled to any period of exclusivity.

5. SUPPLEMENT(s)

Original 11/15/96

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

chlorhexidine Gluconate

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

Amendment 2/29/97
Amendment 5/9/97
Amendment 11/12/97

10. PHARMACOLOGICAL CATEGORY

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

DMF's

13. DOSAGE FORM

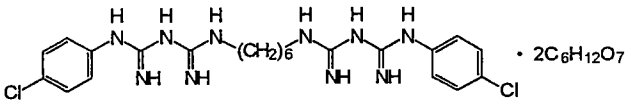
Rinse solution

14. POTENCY

18,0 mg/15 mL (0.12% w/v)

15. CHEMICAL NAME AND STRUCTURE

Chlorhexidine Gluconate. 2,4,11,13-Teraazateradecanediimidamide, *N,N"*-bis(4-chlorophenyl)-3,12-diimino-, di-D-gluconate. $C_{22}H_{30}Cl_2N_{10}\cdot 2C_6H_{12}O_7$. 897.77. 18472-51-0. Antimicrobial. USAN 1993, page 134.



16. RECORDS AND REPORTS

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS
The application is not approvable.

19. REVIEWER: Nashed E. Nashed, Ph.D. DATE COMPLETED:5/18/98
Supervisor: Paul Schwartz, Ph.D.

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of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #1

2. Your analytical methods will be validated by FDA District Laboratory.

Sincerely yours,

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

cc: ANDA 75-006
Division File
Field Copy

Endorsements:

HFD-627/NNashed/5/18/98 5/19/98
HFD-627/PSchwartz/5/18/98 5/19/98
HFD-617/JBuccine/5/19/98 5/19/98
X:\NEW\FIRMSAM\MORTON\LTRS&REV\75006.1
F/t by: gp/5/19/98

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 75-006

3. NAME AND ADDRESS OF APPLICANT

Morton Grove Pharmaceutical, Inc.
6451 West Main Street
Morton Grove, IL 60053

4. LEGAL BASIS FOR SUBMISSION

The firm knows of no patents that claim the reference listed drug product. Also believes that the reference listed drug is not entitled to any period of exclusivity.

5. SUPPLEMENT(s)

Original 11/15/96

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

chlorhexidine Gluconate

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

Amendment 2/29/97
Amendment 5/9/97
Amendment 11/12/97
Amendment 7/10/98

10. PHARMACOLOGICAL CATEGORY

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

DMF's ———————————————

13. DOSAGE FORM

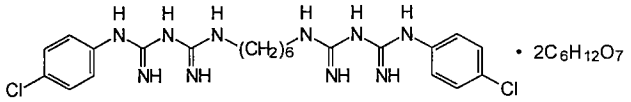
Rinse solution

14. POTENCY

18,0 mg/15 mL (0.12% w/v)

15. CHEMICAL NAME AND STRUCTURE

Chlorhexidine Gluconate. 2,4,11,13-Teraazateradecanediimidamide, *N,N"*-bis(4-chlorophenyl)-3,12-diimino-, di-D-gluconate. $C_{22}H_{30}Cl_2N_{10} \bullet 2C_6H_{12}O_7$. 897.77. 18472-51-0. Antimicrobial. USAN 1993, page 134.



16. RECORDS AND REPORTS

17. COMMENTS

18. CONCLUSIONS AND RECOMMENDATIONS

The application is not approvable – The labeling is deficient and method validation is pending.

19. REVIEWER: Nashed E. Nashed, Ph.D. DATE COMPLETED: 1/12/99

Supervisor: Paul Schwartz, Ph.D. 1/13/99

APPEARS THIS WAY
ON ORIGINAL

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confidential commercial

information from

CHEMISTRY REVIEW #2

38. Chemistry Comments to be provided Comments to be Provided to the Applicant.

ANDA: 75-006 APPLICANT: Morton Grove Pharmaceutical, Inc.

DRUG PRODUCT: Chlorhexidine Gluconate Oral Rinse, 0.12%.

The deficiencies presented below represent FACSIMILE deficiencies.

A. Deficiencies:

Please provide information regarding the dosage cup that is packaged with the bottle and demonstrate that it delivers ½ oz and is so marked.

Sincerely your,

11-10-99

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 75-006
Division File
Field Copy
HFD-600/Reading File

Endorsements:

HFD-627/N.Nashed, Ph.D./1-12-99 1/19/99
HFD-627/P.Schwartz, Ph.D./1-13-99 1/19/99
HFD-617/J.Buccine, PM/1-14-99 1/19/99
\\CDV008\WP51F99\FIRMSAM\MORTON\LTRS&REV\75-006.2.DOC
F/T by: bc/1-14-99

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 75-006

3. NAME AND ADDRESS OF APPLICANT

Morton Grove Pharmaceutical, Inc.
6451 West Main Street
Morton Grove, IL 60053

4. LEGAL BASIS FOR SUBMISSION

The firm knows of no patents that claim the reference listed drug product. Also believes that the reference listed drug is not entitled to any period of exclusivity.

5. SUPPLEMENT(s)

Original 11/15/96

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

chlorhexidine Gluconate

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

Amendment 2/29/97
Amendment 5/9/97
Amendment 11/12/97
Amendment 7/10/98
Amendment 2/9/99
Amendment 3/23/99

10. PHARMACOLOGICAL CATEGORY

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

DMF's ———————————————

13. DOSAGE FORM

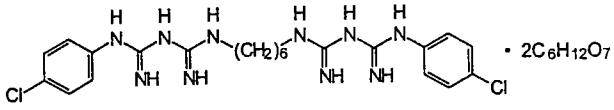
Oral Rinse solution

14. POTENCY

18,0 mg/15 mL (0.12% w/v)

15. CHEMICAL NAME AND STRUCTURE

Chlorhexidine Gluconate. 2,4,11,13-Teraazateradecanediimidamide, *N,N"*-bis(4-chlorophenyl)-3,12-diimino-, di-D-gluconate. $C_{22}H_{30}Cl_2N_{10} \bullet 2C_6H_{12}O_7$. 897.77. 18472-51-0. Antimicrobial. USAN 1993, page 134.



16. RECORDS AND REPORTS

17. COMMENTS

DMF —— is deficient.

The method validation is deficient.

18. CONCLUSIONS AND RECOMMENDATIONS

The application is not approvable .

19. REVIEWER: Nashed E. Nashed, Ph.D. DATE COMPLETED:

4/26/99

Supervisor: Paul Schwartz, Ph.D. 4/28/99

V:\FIRMSAM\MORTON\LTRS&REV\75-006.3.DOC

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of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #3

cc: ANDA 75-006
Division File
Field Copy

Endorsements:

HFD-627/N.Nashed, Ph.D./4-26-99 /N/ 4/28/99
HFD-627/P.Schwartz, Ph.D./4-28-99 /S/ 4/29/99
HFD-617/J.Buccine, PM/4-29-99 JB 4/30/99
V:\FIRMSAM\MORTON\LTRS&REV\75-006.3.DOC
F/T by: bc/4-29-99

1. CHEMISTRY REVIEW NO. 4

2. ANDA # 75-006

3. NAME AND ADDRESS OF APPLICANT

Morton Grove Pharmaceutical, Inc.
6451 West Main Street
Morton Grove, IL 60053

4. LEGAL BASIS FOR SUBMISSION

The firm knows of no patents that claim the reference listed drug product. Also believes that the reference listed drug is not entitled to any period of exclusivity.

5. SUPPLEMENT(s)

Original 11/15/96

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

chlorhexidine Gluconate

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

Amendment 2/29/97
Amendment 5/9/97
Amendment 11/12/97
Amendment 7/10/98
Amendment 2/9/99
Amendment 3/23/99
Amendment 8/23/99

10. PHARMACOLOGICAL CATEGORY

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

DMF's ———————————————————

13. DOSAGE FORM

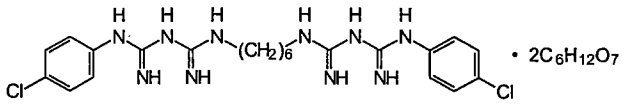
Oral Rinse solution

14. POTENCY

18,0 mg/15 mL (0.12% w/v)

15. CHEMICAL NAME AND STRUCTURE

Chlorhexidine Gluconate. 2,4,11,13-Teraazateradecanediimidamide, *N,N"*-bis(4-chlorophenyl)-3,12-diimino-, di-D-gluconate. $C_{22}H_{30}Cl_2N_{10} \bullet 2C_6H_{12}O_7$. 897.77. 18472-51-0. Antimicrobial. USAN 1993, page 134.



16. RECORDS AND REPORTS

17. COMMENTS

DMF —— is deficient.

18. CONCLUSIONS AND RECOMMENDATIONS

The application is not approvable .

19. REVIEWER: Nashed E. Nashed, Ph.D. DATE COMPLETED: 10/12/99

Supervisor: Paul Schwartz, Ph.D.

\\CDV008\WP51F99\FIRMSAM\MORTON\LTRS&REV\75-006.3.DOC

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confidential commercial

information from

CHEMISTRY REVIEW #4

38. Chemistry Comments to be Provided to the Applicant.

ANDA 75-006 APPLICANT: Morton Grove Pharmaceutical, Inc.

DRUG PRODUCT: Chlorhexidine Gluconate Oral Rinse, 0.12%

The deficiencies presented below represent MINOR deficiencies.

1. DMF ——— for the ——————————— remains deficient. Please do not respond to this amendment until you have been notified by the DMF holder that the DMF deficiencies have been addressed.

2. [redacted]

Sincerely yours,

10/29/99

S.r Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry 1
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 75-006
Division File
Field Copy
Endorsements:
HFD-627/NNashed NN 10/24/99
HFD-627/Pschwartz KWoodland for PS 10/29/99
HFD-617/Jbuccine 10/25/99
\\CDV008\WP51F99\FIRMSAM\MORTON\LTRS&REV\75-006.3.DOC
FT/njg/10/28/99

Not approvable

1. CHEMISTRY REVIEW NO. 5

2. ANDA # 75-006

3. NAME AND ADDRESS OF APPLICANT

Morton Grove Pharmaceutical, Inc.
6451 West Main Street
Morton Grove, IL 60053

4. LEGAL BASIS FOR SUBMISSION

The firm knows of no patents that claim the reference listed drug product. Also believes that the reference listed drug is not entitled to any period of exclusivity.

5. SUPPLEMENT(s)

Original 11/15/96

6. PROPRIETARY NAME

N/A

7. NONPROPRIETARY NAME

chlorhexidine Gluconate

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

Amendment 2/29/97
Amendment 5/9/97
Amendment 11/12/97
Amendment 7/10/98
Amendment 2/9/99
Amendment 3/23/99
Amendment 8/23/99
Miscellaneous correspondence 1/22/03
CMC Amendment 8/1/03
CMC Telephone Amendment 12/11/03
CMC Telephone Amendment 2/10/04

10. PHARMACOLOGICAL CATEGORY

Treatment of gingivitis

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

DMF's

13. DOSAGE FORM

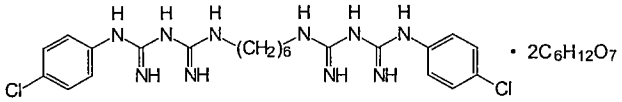
Oral Rinse solution

14. POTENCY

18,0 mg/15 mL (0.12% w/v)

15. CHEMICAL NAME AND STRUCTURE

Chlorhexidine Gluconate. 2,4,11,13-Teraazateradecanediimidamide, *N,N"*-bis(4-chlorophenyl)-3,12-diimino-, di-D-gluconate. $C_{22}H_{30}Cl_2N_{10} \bullet 2C_6H_{12}O_7$. 897.77.



16. RECORDS AND REPORTS

17. COMMENTS

None

18. CONCLUSIONS AND RECOMMENDATIONS

The application is approvable .

N. Nashed

19. REVIEWER: Nashed E. Nashed, Ph.D.

DATE COMPLETED: 12/23/03
Revised Date: 2/23/04 2/27/04

Team Leader: Jams M. Fan

DATE:2/24/04

2/27/04

V:\FIRMSAM\MORTON\LTRS&REV\75-006.4.doc

Redacted 11 page(s)

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confidential commercial

information from

CHEMISTRY REVIEW #5

cc: ANDA 75-006
Division File
Field Copy

Endorsements:
HFD-627/Nnashed/2/23/04 NN 2/27/04
HFD-627/Jfan/2/24/04 2/27/04
HFD-617/Avu/2/26/04 3/04/04

F/T:ard/2/26/04

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-006

BIOEQUIVALENCE REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/~~AABA~~ # 75-006 SPONSOR: Morton Grove
DRUG: Chlorhexidine Gluconate
DOSAGE FORM: Oral Rinse.
STRENGTH(s): 0.12%
TYPE OF STUDY: ~~Single~~/Multiple ~~Fasting~~/~~Fed~~
STUDY SITE: N/A.

STUDY SUMMARY:

Waiver granted under 320.22, formulation Q & Q.

DISSOLUTION:

N/A

PRIMARY REVIEWER: A P. Patel. BRANCH: 3

INITIAL: APPatel DATE: 3/10/98

BRANCH CHIEF: DR. Moheb MAKARY, Ph. D. BRANCH: 3

INITIAL: MM DATE: 3/11/98

DIRECTOR
DIVISION OF BIOEQUIVALENCE

INITIAL: DR DATE: 4/1/98

DIRECTOR
OFFICE OF GENERIC DRUGS

INITIAL: DATE:

Chlorhexidine Gluconate
Oral Rinse, 0.12%
ANDA # 75-006
Reviewer: A.P.Patel
X:\NEW\FIRMSAM\MORTON\LTRS&REV\75006W.597

Morton Grove Pharmaceuticals
Morton Grove, IL
Submission Date:
May 9, 1997 - (11/2/97)

REVIEW OF A WAIVER REQUEST

Background:

On 11/14/96 the firm submitted an application requesting waiver of the in vivo bioequivalence requirements for its chlorhexidine gluconate 0.12% oral rinse. The Agency refused to file the application on the basis that Morton Grove's formulation was not Q and Q to the reference listed drug. The firm now (May 9, 1997) has submitted a new formulation which is Q and Q to the reference listed drug.

Comments:

1. The Office of Generic Drugs (OGD) has determined that a generic version of chlorhexidine gluconate topical oral rinse solution, should be granted a waiver of bioequivalence study requirement when the inactive ingredients (except for those ingredients used exclusively as coloring and flavoring agents), are qualitatively and quantitatively similar to the corresponding inactive ingredients of Peridex® manufactured by Proctor & Gamble.

2. The formulation comparison between the test and reference drug products shows that formulation is Q and Q to the reference listed drug product (attachments).

3. Comparative Formulations: Test and Reference products.

	Test		Peridex®	
Ingredients	%(w/v or v/v)	Test mg/ml	Ref mg/ml	Ref range mg/ml
chlorhexidine gluconate, [redacted]	0.12	1.2	1.2	[redacted]
[redacted] alcohol [redacted]	11.6	[redacted]	[redacted]	[redacted]
Glycerin	[redacted]	[redacted]	[redacted]	[redacted]
PEG-40 sorbitan diisostearate		[redacted]	[redacted]	[redacted]
Sodium saccharin, [redacted]		[redacted]	[redacted]	[redacted]
FD&C Blue No. 1		[redacted]	[redacted]	[redacted]
Peppermint stick flavor	[redacted]			

Recommendations:

1. The Division of Bioequivalence agrees that the information submitted by Morton Grove Pharmaceuticals demonstrates that its reformulated test chlorhexidine gluconate, 0.12% oral rinse falls under 21 CFR Section 320.22 of the Bioavailability/Bioequivalence Regulations. The waiver of the *in-vivo* bioequivalence study for the test product is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test oral rinse formulation to be bioequivalent to Peridex® (chlorhexidine gluconate 0.12%) Oral Rinse manufactured by Proctor & Gamble.

CC: ANDA 75-006
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Secretary - Bio Drug File
HFD-658/ A.P.Patel

Path and File Name: X:\NEW\FIRMSAM\MORTON\LTRS&REV\75006W.597
Printed in final on March 10, 1998.

3/13/98

A.P.Patel
Division of Bioequivalence
Review Branch III

RD INITIALED MMakary
FT INITIALED MMakary Moheb H. Makary Date: 3/11/98
Moheb Makary, Ph.D.
Acting Team Leader,
Review Branch III

Concur: Dale P. Conner Date: 4/1/98
Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence

BIOEQUIVALENCY - ACCEPTABLE

1. **WAIVER** (WAI) Strengths: 0.12%
Outcome: AC

Outcome Decisions:
AC - Acceptable
NC - No Action
UN - Unacceptable (fatal flaw)
IC - Incomplete
WINBIO COMMENTS: waiver granted

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-006

ADMINISTRATIVE DOCUMENTS

RECORD OF TELEPHONE CONVERSATION

See new correspondence 5/9/97 / control# 97-108

Originally Morton Grove Pharmaceuticals submitted a correspondence dated May 9, 1997 as an amendment to a refuse to file action for ANDA 75-006. The main reason for the ANDA not to be filed was that Morton Grove's original formulation was not Q and Q to the reference listed drug, which made it unacceptable to request a wavier of in-vivo bioequivalence. The amendment was converted to an OGD control document #97-108. The firm's correspondence included a new proposed formulation for their Chlorhexidine Gluconate Oral Rinse, 0.12% product. After reviewing the new formulation it was determined that it would be acceptable so the firm could qualify for a waiver of in-vivo bioequivalence requirements.

DATE
May 28, 1997

APPLICATION NUMBER
Control# 97-108 (related to ANDA 75-006)

IND NUMBER

TELECON

INITIATED BY **MADE**
_ APPLICANT/ SPONSOR
_ BY TELE.
X FDA
_ IN PERSON

PRODUCT NAME
Chlorhexidine Gluconate Oral Rinse, 0.12%

FIRM NAME
Morton Grove Pharmaceuticals

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Maurice Bordoni

TELEPHONE NUMBER
847-967-5600

SIGNATURE
Harvey Greenberg
5/28/97

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date FEB 24 2000

From Consumer Safety Officer, Investigations & Preapproval Compliance Branch/DMPQ (HFD-324)

Subject Concurrence with District Withhold Recommendation, ANDAs ———, 75-006, 40-313 75-514 and 75-586

To Pat Beers-Block, Chief
Review Support Branch, HFD-632

Applicant: Morton Grove
Pharmaceuticals, Inc.
6451 West Main St.
Morton Grove, IL 60053
CFN 1420913

Division of Manufacturing and Product Quality (DMPQ) has completed a review of an EIR pertinent to the subject ANDAs. An inspection was conducted at Morton Grove's facility from November 16 - December 16, 1999. The EIR covers the finished product manufacture and testing to be performed at this site for ANDA 75-006 (Chlorhexidine Gluconate Solution .15% Oral Rinse) and covers testing to be performed for ANDA ———. The following ANDAs in the profile class LIQ were not covered during the current inspection, but are also subject to this withhold recommendation -

ANDA 40-313 Prednisolone Syrup, 15mg/5ml

ANDA 75-514 Fluoxetine Hydrochloride For Oral Solution 20mg/5ml

ANDA 75-586 Metaproterenol Sulfate Solution Inhalation, .4% and .6%.

DMPQ concurs with the District's recommendation to withhold approval of the subject ANDAs. Our concurrence with CHI-DO's withhold recommendation is based on the following significant GMP deviations, several of which are recurring deficiencies noted during previous inspections:

- Failure to complete investigations of out-of-specification (OOS) laboratory results. For example, six Morton Grove products were observed to have stability failures (i.e. degradants, potency and specific gravity) during 1999. Five of these failures were confirmed by

further testing, yet no further investigation has been initiated, from one to four months after the failures. Additionally, two of these failures have documents that state "Initiate Investigation". All product batches exhibiting these failures were released or released and distributed. No voluntary recalls have been initiated by Morton Grove.

Failure to complete investigations of stability failures is a repeat GMP deficiency noted on FDA-483s issued at the conclusion of FDA inspections in April 1998 and April 1999 for different products.

- Failure to file field alerts for three of the six products exhibiting out-of-specification stability results.

- A cleaning validation study for nineteen of twenty Morton Grove products is inadequate in that the studies for nineteen of those twenty products have neither been completed nor scheduled.

Failure to complete cleaning validation is a repeat GMP deficiency. It is particularly significant, in that two instances of cross contamination of finished products, attributed to insufficient cleaning procedures, were documented in the previous inspection of March-April, 1999. Furthermore, Morton Grove has twice failed to meet written commitments to CHI-DO in regard to initiating cleaning validation studies;

1) Morton Grove's May 5, 1999 response to CHI-DO's April 12, 1999 FDA-483 committed to an end of June, 1999 time line, for undertaking revalidation of the established method of cleaning.

2) A follow-up response dated July 23, 1999 included another commitment "...to complete implementation..." of the cleaning validation studies "...by December, 1999."

As of mid-December 1999 CHI-DO's EI documented that the cleaning validation for nineteen of twenty Morton Grove products was neither implemented nor scheduled.

- Failure to maintain a procedure for identifying microbial isolates that exceed action or alert specifications in raw material(s) and finished product(s).

CHI-DO observed, during the previous inspection, that Morton Grove had been performing identification of such microbial isolates. This procedure has ceased since the previous inspection, when microbial isolates from samples of six lots of two non-sterile liquid products were documented as exceeding action levels for total plate count. The organism isolated was identified by Morton Grove as Acinetobacter baumanii, an opportunistic gram negative pathogen. Morton Grove, eventually recalled eight lots of products following the previous inspection contaminated with A. baumanii. During the current inspection, Morton Grove's Microbiology Laboratory Manager informed CHI-DO that identifying microbial isolates was never a requirement, but was used for informational purposes.

CHI-DO apprised Morton Grove of these continuing GMP deviations in a warning letter issued January 14, 2000. In view of the OAI status of Morton Grove, the recurring GMP deficiencies, and this applicant's failure to follow through on commitments to correct GMP deficiencies, DMPQ is also extending the withhold recommendation to ANDAs 40-313, 75-514 and 75-586.

A copy of the EIR and exhibits are attached for your review. If you have questions, please contact me at (301)-827-0065.

Randall L. Woods

Randall L. Woods

Attachments - EIR and Exhibits

cc:
HFD-320 R/F
HFD-324 RWoods
HFD-623 JBuccine
HFD-625 MSmela
HFD-629 VSayeed
HFD-645 BArnwine
HFD-640 TAmes
HFR-CE640 RHarrison
HFR-CE695 KHaas
HFR-CE650 LJarrel
NLyons
YLozano
Draft:RLWoods
Concur:BHartman 2/23/00
Final:RLWoods
a:\anda75.422

APPEARS THIS WAY
ON ORIGINAL

RECORD OF TELEPHONE CONVERSATION

Jim Fan called Dr. Gavaskar of Morton Grove today requesting him to submit a statement stating that any extension of their drug product expiration dating should be based on the submission of stability data from three production batches. Dr. Gavaskar has agreed to fax this statement as a telephone amendment to this effect to the attention of Ann Vu followed by a hard copy to the Document Room. The tel. conversation was then concluded.	**DATE:** **2/5/2004**
	ANDA NUMBER 75-006
	TELECON INITIATED BY AGENT OR SPONSOR **FDA**
	PRODUCT NAME: Chlorhexidine Gluconate Oral Rinse, USP
	FIRM NAME: **MORTON GROVE**
	FIRM REPRESENTATIVES: Kaustudh Gavaskar, QA Audit Senior Director
	TELEPHONE NUMBER: 847-967-5600
	FDA REPRESENTATIVES Jim Fan
	SIGNATURES:

Orig: ANDA 75-006
Cc: Division File
Chem. I Telecon Binder
V:\firmsam\Morton\Telecons\75006.04feb2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-006

CORRESPONDENCE

ANDA 75-006

Morton Grove Pharmaceuticals, Inc.
Attention: Maurice E. Bordoni
6451 West Main Street
Morton Grove, IL 60053

JAN 10 1997

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated November 15, 1996, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Chlorhexidine Gluconate Oral Rinse, 0.12%w/v.

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

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

In order to request a waiver of *in vivo* bioequivalence for Chlorhexidine Gluconate Oral Rinse, 0.12%, the inactive ingredients in the proposed product must be qualitatively and quantitatively the same as the reference listed drug. Your proposed product differs both qualitatively and quantitatively from the reference listed drug. Please submit an *in vivo* bioequivalence study. As an alternative you may wish to reformulate your product. You may contact Lizzie Sanchez, Project Manager, Division of Bioequivalence, at (301) 594-2290 for bioequivalence requirements for this product.

Generally, a drug product for topical use shall contain the same inactive ingredients as the reference listed drug in order to request for waiver of evidence of *in vivo* bioequivalence. However an applicant may seek approval of a drug product that differs from the reference listed drug provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety of the proposed drug product [21 CFR 314.94(9)(v)]. Please refer to the Agency's Inactive Ingredient Guide, dated January 1996. In addition, please refer to the Office of Generic Drugs Interim Inactive Ingredients Policy, dated November 17, 1994.

We note that you have provided a qualitative comparison of your proposed formulation with the refrence listed drug. However, you have failed to provide a side-by-side

quantitative comparison of your proposed formulation with the formulation of the reference listed drug product. In addition please characterize and explain any formulation differences, and provide information that these differences do not affect the safety of the proposed drug product. This information to demonstrate safety should include, but is not limited to: (a) examples of approved drug products administered by the same route of administration which contain the same inactive ingredients, and that are within the same concentration range, (b) a description of the purpose of the inactive ingredients when different inactive ingredients are included in the proposed drug product, (c) a comparison of the physical and chemical properties (e.g. pH, viscosity, osmolarity) of the proposed drug product with that of the reference listed drug, and (d) information to show that the inactive ingredients do not adversely affect these properties.

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

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CAR 314.101(a)(3)If you do so, the application shall be filed over protest under 21 CAR 314.101(a)(2). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

Harvey Greenberg
Project Manager
(301) 594-0315

Sincerely yours,

/for 1/10/97

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 75-006
cc: DUP/Jacket
Division File
HFD-93
Field Copy
HFD-600/Reading File
HFD-615/MBennett

Endorsement: HFD-615/PRickman, Acting CPrusch for 1/10/97 date
HFD-615/HGreenberg, CSO HGreen 1/10/97 date
HFD-629/PSchwartz, Chem Branch date
WP File x:\wpfile\greenber\74\75006.rtf
F/T File tdb 01-06-97
ANDA Refuse to File!

ANDA 75-006

Morton Grove Pharmaceuticals, Inc.
Attention: Maurice E. Bordoni
6451 West Main Street
Morton Grove, IL 60053

Dear Sir:

Please refer to your abbreviated new drug application (ANDA) dated November 15, 1996, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Chlorhexidine Gluconate Oral Rinse, 0.12%w/v.

Reference is also made to our "Refuse to File" dated January 10, 1997, and your amendment dated January 29, 1997.

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

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

As we stated in our previous letter, in order to request a waiver of *in vivo* bioequivalence for Chlorhexidine Gluconate Oral Rinse, 0.12%, the inactive ingredients in the proposed product must be qualitatively and quantitatively the same as the reference listed drug. Your proposed product differs both qualitatively and quantitatively from the reference listed drug. Your components and composition statement indicates that your product contains sodium citrate, and citric acid, the reference listed drug does not contain these inactive ingredients. In addition your formulation appears to be quantitatively different (i.e., the quantity of the inactive ingredients varies by more than +/- 5%) from the reference listed drug for the following inactive ingredients: _____ Therefore, you are required to provide evidence of *in vivo* bioequivalence. Please submit an *in vivo* bioequivalence study. Please refer to the Division of Bioequivalence's document regarding the requirements for a waiver of *in vivo* bioequivalence, as revised March 29, 1993. You can obtain this document through the FDA Fax-on-Demand System at 1-800-342-2772. As an alternative you may wish to reformulate your product to be qualitatively and

quantitatively the same as the reference listed product. This reformulation would then qualify your product to be considered for a waiver of *in vivo* bioequivalence. You may contact Lizzie Sanchez, Project Manager, Division of Bioequivalence, at (301) 594-2290 for information regarding the current *in vivo* bioequivalence requirements for this product.

If you plan to reformulate your product and wish to obtain the Office of Generic Drugs' opinion regarding the acceptability of your revised formulation, please submit your revised formulation to the attention of Douglas L. Sporn, Director, Office of Generic Drugs with a request for opinion and we will review your request.

In future submissions for topical drug products please provide a side-by-side qualtitative and quantititative comparison of your formulation with that of the reference listed drug in the bioequivalence section of your application. In addition, please use a consistent expression of your composition for the proposed drug product. For example, please express all quantities of inactive ingredients as mg/mL or %w/w.

Please provide a revised letter of authorization from ——— which grants the FDA access to reference the drug master file # ——— for chlorhexidine gluconate ——————— in support of any applications filed for chlorhexidine gluconate from Morton Grove Pharmaceuticals.

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

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(a)(3) If you do so, the application shall be filed over protest under 21 CAR 314.101(a)(2). The filing date will be 60 days after the date you requested the informal conference.

If you have any questions please call:

Harvey Greenberg
Project Manager
(301) 827-5862

Sincerely yours,

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

ANDA 75-006
cc: DUP/Jacket
Division File
HFD-93
Field Copy
HFD-600/Reading File
HFD-615/MBennett

Endorsement: HFD-615/PRickman, Chief RSB [signature] date 5/1/97
HFD-615/HGreenberg, CSO [signature] 4/28/97 date
HFD-629/PSchwartz, Chem Branch date
WP File x:\wpfile\greenber\75\75006b.rtf
F/T File tdb 04-16-97
ANDA Refuse to File!

APPEARS THIS WAY
ON ORIGINAL

May 9, 1997

Via Federal Express

Morton Grove Pharmaceuticals, Inc.
6451 West Main Street
Morton Grove, Illinois 60053
Phone (847) 967-5600
Fax (847) 967-2211

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

NEW CORRESP

NC

ANDA # 75-006
Chlorhexidine Gluconate Oral Rinse

Re: Amendment in Response to Deficiency Letter Phillips to Bordoni, dated May 1, 1997

Dear Mr. Sporn:

Pursuant to Jerry Phillips' May 1, 1997, letter (copy enclosed), Morton Grove Pharmaceuticals, Inc., (MGP) is amending the above application. A complete copy of this amendment is being sent to the Chicago District Office, FDA, and to Jerry Phillips, Director, Division of Labeling and Program Support, OGD. For your convenience, our response is preceded by your comment.

If you need further information, please contact me at 847-967-5600.

Sincerely,

Albert J. Mueller for

Maurice E. Bordoni
Vice President, Regulatory Affairs

RECEIVED
MAY 12 1997
GENERIC DRUGS

000003

November 12, 1997

Via Federal Express

Morton Grove Pharmaceuticals, Inc.
6451 West Main Street
Morton Grove, Illinois 60053
Phone (847) 967-5600
Fax (847) 967-2211

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

NDA ORIG AMENDMENT
N/AC

RECEIVED
NOV 14 1997
GENERIC DRUGS

ANDA # 75-006
Chlorhexidine Gluconate Oral Rinse
Product Code 8154

Re: Reformulation Amendment in Response to Refusal to File Letter, Phillips to Bordoni, dated May 1, 1997

Dear Mr. Sporn:

Pursuant to Jerry Phillips's May 1, 1997, letter (copy enclosed), Morton Grove Pharmaceuticals, Inc., (MGP) is amending the above application. A complete copy of this amendment is being sent to the Chicago District Office, FDA, and to Jerry Phillips, Director, Division of Labeling and Program Support, OGD.

Note: For our reformulation exhibition batches for **Chlorhexidine Gluconate Oral Rinse**, we decided to issue a new product code—8154—to avoid confusion between the original formulation submitted (Product Code 8109) and the new formulation.

Because **Chlorhexidine Gluconate Oral Rinse** has been adjudged to be a topical solution, the product must have the same excipients in the same concentrations as the reference listed drug. We are submitting a new formulation that meets those criteria.

If you need further information, please contact me at 847-967-5600.

Sincerely,

Maurice E. Bordoni

Maurice E. Bordoni
Vice President, Regulatory Affairs
and Regulatory Compliance

ANDA 75-006

Morton Grove Pharmaceuticals, Inc.
Attention: Maurice E. Bordoni
6451 West Main Street
Morton Grove, IL 60053

APR 16 1998

Dear Sir:

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 also made to our "Refuse to File" letters dated January 10, and May 1, 1997 and your amendment dated November 12, 1997.

NAME OF DRUG: Chlorhexidine Gluconate Oral Rinse, 0.12%

DATE OF APPLICATION: November 15, 1996

DATE OF RECEIPT: November 19, 1996

DATE ACCEPTABLE FOR FILING: November 14, 1997

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

If the above methodology is not submitted, the review of the application will be delayed.

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

Should you have questions concerning this application, contact:

Joe Buccine
Project Manager
(301) 827-5848

Sincerely yours,

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 75-006
cc: DUP/Jacket
Division File
Field Copy
HFD-610/J.Phillips
HFD-92
HFD-615/M.Bennett

Endorsement: HFD-615/PRickman, Chief, RSB _____ date 4/16/98
HFD-615/HGreenberg,CSO _____ date
HFD-629/PSchwartz,Sup. Chem _____ date
WP File x:/new/firmsam/morton/ltrs&rev/75006.ack
F/T/mjl/4/14/98
ANDA Acknowledgement Letter!

MAJOR AMENDMENT

MAY 28 1998

ANDA 75-006

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: Morton Grove Pharmaceutical, Inc. PHONE: 847 967 5600

ATTN: Maurice Bordoni FAX: 847 967 2211

FROM: Joseph Buccine PROJECT MANAGER (301) 827–5848

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated November 15, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Chlorhexidine Gluconate Oral Rinse, 0.12% w/v.

Reference is also made to your amendment dated November 12, 1997.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (8 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 MAJOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MAJOR 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 this represents a second or greater occasion upon which significant (MAJOR) deficiencies have been identified, please contact the Project Manager within 30 days for further clarification or assistance.

SPECIAL INSTRUCTIONS:

Chemistry, labeling and bioequivalence comments are provided.

OK Pmbo 5/27/98

X:\new\ogdadmin\macros\faxmaj.frm

BIOEQUIVALENCY COMMENTS

ANDA: 75-006 APPLICANT: Morton Grove Pharmaceuticals

DRUG PRODUCT: Chlorhexidine gluconate, 0.12% oral rinse

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

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 Conner

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

MAY 28 1998

38. Chemistry Comments to be Provided to the Applicant.

ANDA: 75-006 APPLICANT: Morton Grove Pharmaceuticals, Inc.

DRUG PRODUCT: Chlorhexidine Gluconate Oral Rinse, 0.12%

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

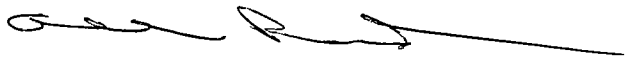
1. [redacted]
2
3
4.
5.
6.
7.
8.
9.

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

1. The firms referenced in your application regarding the manufacturing and testing of the drug product should be in compliance with CGMPs at the time of the approval

2. Your analytical methods will be validated by FDA District Laboratory.

Sincerely yours,



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

July 10, 1998

Via Federal Express

Morton Grove Pharmaceuticals, Inc.
6451 West Main Street
Morton Grove, Illinois 60053
Phone (847) 967-5600
Fax (847) 967-2211

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

CHEM AMENDMENT

N/AC

ANDA # 75-006
Chlorhexidine Gluconate Oral Rinse, 0.12% w/v

Re: Major Amendment in Response to Deficiency Letter, Patel, Phillips, and Conner to Bordoni, dated May 28, 1998

Dear Mr. Sporn:

Pursuant to the Deficiency Letter (copy enclosed) from Rashmikant M. Patel, Jerry Phillips, and Dale Conner, dated May 28, 1998, Morton Grove Pharmaceuticals, Inc., (MGP) is amending the above application. A complete copy of this amendment is being sent to the Chicago District Office, FDA; Rashmikant M. Patel, Ph.D., Director, Division of Chemistry I, OGD; and to Jerry Phillips, Director, Division of Labeling and Program Support, OGD. Because the Division of Bioequivalence has completed its review and has no questions at this time, a copy of this response is not being sent to Dale Conner, Pharm. D., Director of Bioequivalence, OGD.

For your convenience, our responses are preceded by your comments.

If you have any further questions, please call me at 847-967-5600.

Sincerely,

Maurice E. Bordoni
Vice President, Regulatory Affairs

RECEIVED
JUL 14 1998
GENERIC DRUGS

004

JAN 22 1999

38. Chemistry Comments to be provided Comments to be Provided to the Applicant.

ANDA: 75-006 APPLICANT: Morton Grove Pharmaceutical, Inc.

DRUG PRODUCT: Chlorhexidine Gluconate Oral Rinse, 0.12%.

The deficiencies presented below represent FACSIMILE deficiencies.

A. Deficiencies:

Please provide information regarding the dosage cup that is packaged with the bottle and demonstrate that it delivers ½ oz and is so marked.

Sincerely your,

for 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

February 9, 1999

Via Federal Express

Morton Grove Pharmaceuticals, Inc.
6451 West Main Street
Morton Grove, Illinois 60053
Phone (847) 967-5600
Fax (847) 967-2211

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

FA
NDA ONG AMENDMENT

ANDA # 75-006
Chlorhexidine Gluconate Oral Rinse, 0.12% w/v

Re: Facsimile Amendment in Response to Deficiency Letter, Patel, and West to Bordoni, dated January 22, 1999

Dear Mr. Sporn:

Pursuant to the deficiency letter (copy enclosed) from Rashmikant M. Patel, and Robert L. West, dated January 22, 1999, Morton Grove Pharmaceuticals, Inc., (MGP) is amending the above application. A complete hard copy of this facsimile amendment is being sent to the Chicago District Office, FDA; Rashmikant M. Patel, Ph.D., Director, Division of Chemistry I, OGD; and to Robert L. West, M.S., R.Ph., Director, Division of Labeling and Program Support, OGD.

For your convenience, our responses are preceded by your comments.

If you have any further questions, please call me at 847-967-5600.

Sincerely,

Kamel F. Egbaria, Ph.D.
Vice President, Research and Development

006

February 9, 1999

Via Federal Express

Morton Grove Pharmaceuticals, Inc.
6451 West Main Street
Morton Grove, Illinois 60053
Phone (847) 967-5600
Fax (847) 967-2211

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

NEW CORRES FPL
No

ANDA # 75-006
Chlorhexidine Gluconate Oral Rinse, 0.12% w/v

Re: Facsimile Amendment in Response to Deficiency Letter, Patel, and West to Bordoni, dated January 22, 1999

Dear Mr. Sporn:

Pursuant to the deficiency letter (copy enclosed) from Rashmikant M. Patel, and Robert L. West, dated January 22, 1999, Morton Grove Pharmaceuticals, Inc., (MGP) is amending the above application. A complete hard copy of this facsimile amendment is being sent to the Chicago District Office, FDA; Rashmikant M. Patel, Ph.D., Director, Division of Chemistry I, OGD; and to Robert L. West, M.S., R.Ph., Director, Division of Labeling and Program Support, OGD.

For your convenience, our responses are preceded by your comments.

If you have any further questions, please call me at 847-967-5600.

Sincerely,

Kamel F. Egbaria, Ph.D.
Vice President, Research and Development

006

March 12, 1999

Via Facsimile & Federal Express

Morton Grove Pharmaceuticals, Inc.
6451 West Main Street
Morton Grove, Illinois 60053
Phone (847) 967-5600
Fax (847) 967-2211

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

NEW CORRESP

NC

ANDA # 75-006
Chlorhexidine Gluconate Oral Rinse, 0.12% w/v

Re: Telephone Amendment

Dear Mr. Sporn:

Pursuant to a telephone call received today from Joseph M. Buccine regarding completion of the FDA's methods validation on this product, Morton Grove Pharmaceuticals, Inc., hereby commits to cooperate with FDA to resolve any methods validation issues that may be revealed when the methods validation is completed.

If there should be any questions, please contact me at 847-967-5600. Thank you for your cooperation.

Sincerely,

Kamel F. Egbaria, Ph.D.
Vice President
Research and Development

RECEIVED
MAR 15 1999
GENERIC DRUGS

March 23, 1999

Via Facsimile & Federal Express

Morton Grove Pharmaceuticals, Inc.
6451 West Main Street
Morton Grove, Illinois 60053
Phone (847) 967-5600
Fax (847) 967-2211

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

NEW CORRESP
NC

ANDA # 75-006
Chlorhexidine Gluconate Oral Rinse, 0.12% w/v

Dear Mr. Sporn:

Pursuant to a telephone request from Paul Schwartz, OGD, Division of Chemistry I, received Monday, March 22, 1999, enclosed are OVI Statements from the two active raw material sources, _____ and _____.

A copy of this letter is being sent to Mr. Schwartz and to the Chicago District Office, FDA.

If there are any questions, please contact me at 847-967-5600. Thank you for your cooperation.

Sincerely,

Kamel F. Egbaria, Ph.D.
Vice President
Research and Development

RECEIVED
MAR 24 1999
GENERIC DRUGS

MINOR AMENDMENT

MAY - 3 1999

ANDA 75-006

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: Morton Grove Pharmaceuticals, Inc. PHONE: 847 967 5600

ATTN: Kamel F. Egbaria FAX: 847 967 2211

FROM: Joseph Buccine PROJECT MANAGER (301) 827–5848

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated November 15, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Chlorhexidine Gluconate Oral Rinse, 0.12%.

Reference is also made to your amendment(s) dated July 10, 1998 and February 9, 1999.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (2 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:

Chemistry comments are provided.

X:\new\ogdadmin\macros\faxmin.frm

Redacted 2 page(s)

of trade secret and/or

confidential commercial

information from

5/3/1999 FDA FAX

ORIGINAL

August 23, 1999

Morton Grove Pharmaceuticals, Inc.
6451 West Main Street
Morton Grove, Illinois 60053
Phone (847) 967-5600
Fax (847) 967-2211

Via Federal Express

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

ORIG AMENDMENT

ANDA # 75-006
Chlorhexidine Gluconate Oral Rinse, 0.12% w/v

Re: Minor Amendment in Response to Deficiency Letter, Patel to Egbaria, dated May 3, 1999

Dear Mr. Sporn:

Pursuant to the deficiency letter (copy enclosed) from Patel to Egbaria, dated May 3, 1999, Morton Grove Pharmaceuticals, Inc., (MGP) is amending the above application. A complete copy of this minor amendment is being sent to the Chicago District Office, FDA and to Rashmikant M. Patel, Ph.D., Director, Division of Chemistry I.

For your convenience, our responses are preceded by your comments.

If you have any further questions, please call me at 847-967-5600.

Sincerely,

Yogita Desai
Manager, Regulatory Affairs

Enclosure

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
AUG 24 1999
OGD

NOV 1 1999

38. Chemistry Comments to be Provided to the Applicant.

ANDA 75-006 APPLICANT: Morton Grove Pharmaceutical, Inc.

DRUG PRODUCT: Chlorhexidine Gluconate Oral Rinse, 0.12%

The deficiencies presented below represent MINOR deficiencies.

1.

2.

Sincerely yours,

for Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry 1
Office of Generic Drugs
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

Chicago District
300 S. Riverside Plaza, Suite 550 South
Chicago, Illinois 60606
Telephone: 312-353-5863

January 14, 2000

WARNING LETTER
CHI-11-00

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. Brian A. Tambi, President/CEO
Morton Grove Pharmaceuticals, Inc.
6451 W. Main Street
Morton Grove, IL 60053

Dear Mr. Tambi:

During an inspection of your drug manufacturing facility located at the above address, conducted from November 16, 1999 through December 16, 1999, FDA investigators Yvonne Lozano and Nicholas Lyons found serious deviations from the current Good Manufacturing Practice Regulations (cGMP)(Title 21, Code of Federal Regulations, Parts 210 and 211). These deviations cause your drug products to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) as follows:

- Failure to conduct sufficiently thorough and adequately detailed investigations as required by 21 CFR 211.192. For example:

  a. The stability failure investigations for Clindamycin Phosphate Topical Solution, lots 21796 and 22334, were not complete in that there was no documented action plan, conclusion, or corrective action, and the investigation did not extend to other batches which may be associated with the identified degradant problem.

  b. The stability failure investigation for Tretinoin Topical Solution, lot 22494, was not complete in that there was no documented action plan, conclusion, or corrective action, and the investigation did not extend to other batches which may be associated with the identified degradant problem.

  c. The stability failure investigation for Myphetane DC-CS, lot 21674, was not complete in that there was no documented action plan, conclusion, or corrective action, and the investigation did not extend to other batches which may be associated with the identified codeine potency problem.

- Failure to conduct sufficient cleaning validation as required by 21 CFR 211.100. The previous inspection conducted from March 3, 1999 to April 12, 1999, documented cross-contamination of drug products which was attributed to insufficient cleaning procedures. In your May 5, 1999 response to the FDA-483

dated April 12, 1999, you stated "....validation studies...will be undertaken to revalidate the established method. The timeline...is end of June, 1999..." You wrote a follow-up response dated July 23, 1999, in which you stated, "...we expect to complete implementation by December, 1999." The current inspection revealed that cleaning validations for 19 of 20 products have not been completed nor scheduled.

- Failure to establish sufficient production and process control procedures as required by 21 CFR 211.100(a) and failure to follow established procedures as required by 21 CFR 211.100(b). The effects of in-process changes on the established/validated process are not considered prior to implementing the changes. For example:

  a. [redacted] tubing was used instead of the [redacted] tubing (as authorized in the established process) in filling lot 22454. The batch was later rejected due to an [redacted].

  b. Batch 22687, Triamcinolone Acetonide Lotion 1%, was [redacted]

- Failure to establish procedures to assure the absence of objectionable microorganisms as required by 21 CFR 211.113(a). The established procedures for investigating microbiological out of specification results do not require identification of microbial isolates. A laboratory procedure for the identification of microbial isolates has not been established as required by 21 CFR 211.160.

The above list of violations is not intended to be an all-inclusive list of deficiencies at your firm. It is your responsibility to ensure that all of your firm's products are in compliance with all requirements of the Act and its implementing regulations. Federal agencies are advised of the issuance of all Warning Letters about drugs and devices so that they may take this information into account when considering the award of contracts.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. These include seizure and/or injunctions.

You should notify this office in writing, within 15 working days of receipt of this letter, of the specific steps you have taken to correct the noted violations, including an explanation of each step being taken to prevent the recurrence of similar violations. If corrective action cannot be completed within 15 working days, state the reason for the

delay and the time within which corrections will be completed. Your response should be addressed to: Richard Harrison, Compliance Director, at the address provided in the letterhead.

Sincerely,

Raymond V. Mlecko
District Director

cc: Sanjeev Bahl, Director, Quality Assurance
Vice President/Regulatory Affairs
Morton Grove Pharmaceuticals, Inc.
6451 W. Main Street
Morton Grove, IL 60053

ANDA 75-006

CERTIFIED MAIL-RETURN RECEIPT REQUESTED

JAN -2 2003

Morton Grove Pharmaceuticals, Inc.
Attention: Yogita Desai
6451 West Main Street
Evanston, IL 60053

Dear Madam:

This letter is in reference to your Abbreviated New Drug Application (ANDA) dated November 15, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Chlorhexidine Gluconate Oral Rinse, 0.12%.

We refer you to our "Not Approvable" letter dated November 1, 1999, which detailed the deficiencies identified during our review of your ANDA. The Agency may consider an ANDA applicant's failure to respond to a "Not Approvable" letter within 180 days to be a request by the applicant to withdraw the ANDA under 314.120(b). Your amendment to the application is overdue. You must amend your application within 10 days of receipt of this letter. Otherwise, an action to withdraw the application will be initiated per 21 CFR 314.99.

If you do not wish to pursue approval of this application at this time, you should request withdrawal in accord with 21 CFR 314.65. A decision to withdraw the application would be without prejudice to refiling.

If you have further questions you may contact Martin H. Shimer, Project Manager, Regulatory Support Branch, at (301) 827-5862.

Please send all correspondence to the following address:

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

Sincerely yours,

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

cc: ANDA # 75-006
DUP/Division File
HFD-610/PRickman
Endorsement:
HFD-617/Gregg Davis, Chief, RSB
HFD-617/MShimer, CSO, 2-1-03

V:\FIRMSAM\MORTON\LTRS&REV\75006.OTH

F/T by cll/12/31/02

10 DAY LETTER!

APPEARS THIS WAY
ON ORIGINAL

January 22, 2003

ORIGINAL

Via Federal Express

New Corr.

ORIG AMENDMENT

N/NC

Regulatory Affairs
Morton Grove Pharmaceuticals, Inc.
6451 West Main Street
Morton Grove, Illinois 60053
Phone (847) 967-5600
Fax (847) 583-5052

1/29/04 received

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

Re: ANDA #75-006, Chlorhexidine Gluconate Oral Rinse, 0.12%
(MGP Product Code: 8154)
Minor Amendment in Response to FDA Letters

- **Patel, FDA to Desai, MGP dated November 1, 1999**
- **Rickman, FDA to Desai, MGP dated January 2, 2003**
- **Final Approval Requested**

Dear Mr. Buehler,

The sponsor, Morton Grove Pharmaceuticals, Inc., (MGP) hereby submits this minor amendment in response to FDA letters (copies enclosed):

- Patel, FDA to Desai, MGP dated November 1, 1999
- Rickmam, FDA to Desai. MGP dated January 2, 2003

MGP is also requesting final approval for this product.

A complete copy of this amendment is being sent to Mr. Arlyn H. Baumgarten, Director, Chicago District Office, FDA.

If you have any questions, please call me at 847-967-5600.

Sincerely,

Yogita Desai

Yogita Desai, Ph.D.
Senior Director
Regulatory Affairs

Encl.

RECEIVED
JAN 23 2003
OGD / CDER

August 1, 2003

Regulatory Affairs
Morton Grove Pharmaceuticals, Inc.
6451 West Main Street
Morton Grove, Illinois 60053
Phone (847) 967-5600
Fax (847) 583-5052

ORIG AMENDMENT
N/AC

Via Federal Express

ORIGINAL

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

Re: ANDA #75-006, Chlorhexidine Gluconate Oral Rinse, 0.12%
(MGP Product Code: 8154)
CMC Amendment

Dear Mr. Buehler,

The sponsor, Morton Grove Pharmaceuticals, Inc., (MGP) hereby submits this CMC amendment to provide an update regarding the analytical method 8154B, Determination of degradants/impurities of Chlorhexidine Gluconate in Raw Material and Chlorhexidine Gluconate Oral Rinse, 0.12%.

A complete copy of this amendment is being sent to Mr. Arlyn H. Baumgarten, Director, Chicago District Office, FDA.

If you have any questions, please call me at 847-967-5600.

Sincerely,

Yogita Desai, Ph.D.
Senior Director
Regulatory Affairs

RECEIVED
AUG 0 4 2003
OGD/CDER

000001

December 11, 2003

ORIG AMENDMENT
N/A

Regulatory Affairs
Morton Grove Pharmaceuticals, Inc.
6451 West Main Street
Morton Grove, Illinois 60053
Phone (847) 967-5600
Fax (847) 583-5052

Via Federal Express

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

ORIGINAL

Re: ANDA #75-006, Chlorhexidine Gluconate Oral Rinse, USP
(MGP Product Code: 8154)
CMC Telephone Amendment

Dear Mr. Buehler,

The sponsor, Morton Grove Pharmaceuticals, Inc. (MGP), hereby submits a CMC telephone amendment to address the comments from FDA review team in a telephonic conference on December 3, 2003.

A complete copy of this amendment is being sent to Mr. Arlyn H. Baumgarten, Director, Chicago District Office, FDA.

If you have any questions, please call me at 847-967-5600.

Sincerely,

Kavita Srivastava
Kavita Srivastava, M.S.
Supervisor
Regulatory Affairs

RECEIVED
DEC 12 2003
OGD/CDER