CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

73695

CORRESPONDENCE

MAR 12 1991

ANDA 73-695

Colgate Palmolive Company
Attention: Craig E. Hammes
909 River Rd
Piscataway, NJ 08855-1343

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 for the following:

NAME OF DRUG: Chlorhexidine Gluconate Oral Rinse, 0.12%

DATE OF APPLICATION: December 13, 1990

DATE OF RECEIPT: December 31, 1990

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

However, in the interim, please submit three additional copies of the analytical methods and descriptive information needed to perform the tests on the samples (both the bulk active ingredient(s) and finished dosage form) and validate the analytical methods. Please do not send samples unless specifically requested to do so. If samples are required for validation, we will inform you where to send them in a separate communication.

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.

Sincerely Yours,

/S/ 3-12-91

Roger L. Williams, M.D.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA #73-695
DUP/Division File
HFD-634/RPatel/2-28-91
HFD-632/RPollock/JDawson/2-28-91
HFD-600/Reading File
R/D initialed by GJohnston
73695ack.ltr(acknow)/jmk/2-28-91
JHanney 3/11/91 3/11/91
Acknowledgement letter
3/11/91

ANDA 73-695

MAY 26 1992

Colgate-Palmolive Company
Attention: Craig E. Hammes
909 River Road
Piscataway, NJ 08854-5596

Dear Sir:

Please refer to your abbreviated new drug application dated December 13, 1990, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Chlorhexidine Gluconate Oral Rinse, 0.12%.

The application is deficient and therefore not approvable under Section 505 of the Act for the following reasons:

1. Please clearly identify the specific responsibilities of Colgate-Palmolive Company and with respect to the manufacture, control and release of the drug product as specified by this ANDA.

2. Please submit specification, test methodology and validation data for Related Substances in the drug substance. Please also submit methods validation data for the drug substance assay.

3. Please provide completed analytical data sheets and manufacturers'(suppliers') certificates of analysis for the drug substance and all excipients used.

4. Concerning the manufacturing process, please submit the following:

   A. A statement as to what your expected or goal yield is for drug product production.

   B. An explanation regarding a theoretical yield of only bottle units from a production batch size of lbs. of drug product. Please explain and account for the remaining % of product.

   C. A summarized clear description and size of each piece of equipment used for product production.

   D. A statement concerning what happens with final drug product material when specification requirements are not achieved.

5. Please provide manufacturers' specifications and their certificates of analysis for the container component materials.

6. Concerning laboratory controls, please provide the following:

   A. the actual product yield obtained for Batch #82259,

   B. the appropriate analytical data obtained for the in-process samples taken for Batch #82259 as stated in the manufacturing procedure in vol. 1.2, page 98, steps and as revised on page 101, steps

   C. executed batch records for Batch #s 82260 and 82261, appropriate analytical data for the respective in-process samples taken, and product yields obtained for these batches, and

   D. release specification limits, test methodology and method validation data for Related Substances in the final drug product.

7. Long-term stability study reports for the production-scale batches, vol. 1.2, pages 181 to 183, give data for only 0 and 24 months; data for all intermediate stations are omitted. Also, no data are given to support the Microbiological Contamination results. Please explain.

8. Accelerated stability study reports for the three pilot-scale batches, pages 186 to 188, show Adequacy of Preservation results, but no raw data to support these findings. Also, no data are given to show preservative effectiveness at the lowest level of preservative. Please provide thess data.

9. Please submit information concerning batch records, manufacturing location, equipment used, and analyses for the pilot-scale batches prepared.

10. It is stated that batch size for the pilot-scale batches was Kg. Please be informed that based on your stated intended regular production size of lbs., the above pilot-scale size is slightly less than one-half the minimum required level for acceptance.

    In order to accept the pilot-scale batch accelerated stability data in support of the two year expiration dating, then you must commit to reduce your regular commercial production size to lbs.

If the long-term stability data for the production-scale batches is used as the basis for product stability support, then you must provide the missing data for all the intermediate test stations as described in Section 7 above.

Please comment and advise accordingly.

11. Concerning stability, please revise your stability information according to the following:

    A. Clearly state and place the following items on your stability study data reporting forms:

        1. Name of product being studied, batch (or lot) number, batch (or lot) size, and date and place of manufacture of product.

        2. Manufacturer of the drug substance.

        3. Brief description of the type and size of container and closure components used for the drug product and container position during storage.

        4. Identity of storage conditions which includes the actual observed temperature during storage. FDA recommends 25-30°C for long-term studies and 40°C for accelerated studies.

        5. Data for all test parameters and test stations for which protocol specifies showing dates of testing. Recommended test stations for long-term stability are 0, 3, 6, 9, 12, 18, 24, 36, 48, and 60 months. Recommended test stations for accelerated studies are 0, 1, 2, 3 months. Separate forms for long-term and accelerated studies are suggested.

    B. Stability protocol is to include a commitment that the first three commercial production batches will be placed on long-term stability study and one batch annually thereafter.

12. Your application fails to include satisfactory labeling information.

In this regard:

A. General Comments

1. The strength of the product should appear at the end of the coined established name.

   Chlorhexidine Gluconate Oral Rinse, 0.12%

   The entire name should appear in the same style of print.

2. We note you have not submitted carton labeling. How is the package insert attached to the immediate container?

3. Please revise your labels and labeling to reflect the amount of alcohol in your product as a percent volume/volume of absolute alcohol.

B. Container Label (18 fl oz) - Not Satisfactory

1. Refer to comment A. 1. under General Comments.

2. We refer you to 21 CFR 201.1(h)(5) for the proper way of expressing the relationship between the manufacturer and distributor (i.e., Manufactured for_____ by _____.)

3. Is the bottle cap marked for a 1/2 fl oz dose or to a "fill line", as is the listed drug?

4. fl oz rather than FL. OZ.

5. Please clarify your instructions to the consumer about opening the bottle. Where does he/she squeeze (cap or bottle)? These directions should be in bold print.

6. We encourage you to indicate the volume of the solution in the bottle in milliliters as the prime expression of potency next to the fluid ounces i.e., 540 mL (18 fl oz).

7. Add the dispensing directions for the pharmacist below "Place Pharmacy Label Here":

   Dispense in original container or in amber glass.

C. Package Insert - Not Satisfactory

1. General Comment

   a. See comment A. 1. under General Comments.

   b. We reserve final comment until the bioequivalency review has been completed.

2. DESCRIPTION

   a. Change to "structural formula".

   b. Include the molecular weight and molecular formula.

3. CLINICAL PHARMACOLOGY

   a. Paragraph 2, line 1 - Delete

   b. Paragraph 2, line 4 should read:

      ...after chlorhexidine gluconate use...

   c. Pharmacokinetics is not a section. The subsection heading should be less prominent than your section headings.

   d. Pharmacokinetics, lines 2 and 3 should read:

      ...the active ingredient is retained... (delete "chlorhexidine gluconate")

4. INDICATIONS AND USAGE rather than INDICATION

5. WARNINGS, paragraph 1

   a. Line 3 - Delete

   b. Line 4 - Rephrase to read:

      ...known if chlorhexidine gluconate use results...

6. PRECAUTIONS

   a. The subsection headings should be properly denoted so they do not appear the same as section headings.

b. General

i. Item #2

a) Paragraph 1, line 4 - Delete

b) Paragraph 1, line 6 - Delete

c) Paragraph 3, line 2

"stain" rather than

ii. Item #3

a) Line 2 - Delete

b) Line 3 should read:

...continued use of Periogard...

c) Line 4 - Delete

c. Usage in Pregnancy

i. Line 6 should read:

...ingesting 30 mL (2 capfuls) of...

ii. Revise the subsection heading to be in accord with 21 CFR 201.57(f)(6).

d. Nursing Mothers, paragraph 2 last line should read:

...ingesting 30 mL (2 capfuls) of...

e. Carcinogenesis, Mutagenesis, Impairment of Fertility

i. Add "Impairment of Fertility" to the subsection heading.

ii. Relocate this subsection so it appears after the subsection "General" (Refer to 21 CFR 201.57 (f).

iii. Paragraph 2, line 1- Italicize or underline "in vivo".

7. ADVERSE REACTIONS

a. Paragraph 1, lines 1 and 2 should read:

...with chlorhexidine gluconate oral rinses are... (delete

b. Paragraph 2, line 2 - Delete

c. Paragraph 3, line 2 - Delete

8. HOW SUPPLIED

The distributor's and manufacturer's name should appear the same as they appear on the container labels. (Refer to comment 2. under Container)

Provide the following:

A. Please revise your labels and labeling.

B. Prepare and submit draft copies of insert labeling and final printed container labels for our review and comment.

13. The following is provided for your information:

A. Please revise your Environmental Assessment Report to comply with requirements of 21 CFR 25.31a. Be advised that you may be eligible for a categorical exclusion to provide an Environmental Assessment Report under 21 CFR 25.24(c)(1).

B. Please submit a certified statement that your operations in the manufacture of the subject drug product as described in this applicantion are in compliance with all applicable Federal, State and local environmental regulations.

C. Firms referenced in the application relative to the manufacturing and testing of the product must be in compliance with CGMPs at the time of approval. We will request an evaluation from the Division of Manufacturing and Product Quality at the appropriate time.

D. Your methods validation is being conducted by our district laboratory and is under review. You will be informed if any deficiencies arise.

The file 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 the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a major amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/

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

cc: ANDA #73-695
#73-695/Division File
HFC-130/JAllen
HFD-600/Reading File
HFD-638/K.Shah
HFD-633/J.Dawson/CSO/4-15-92
HFD-633/DJames
R/D initialed by PSchwartz, Ph.D./4-9-92
R/D by D.James, Ph.D. B:\73695RL1.DJ
R/D MM 4-15-92

NOT APPROVABLE - Major Amendment

Chlorhexidine Gluconate, 0.12%
(PerioGard®)
ANDA 73-695

Mr. Craig E. Hammes
Corporate Director
Regulatory and Government Affairs
Colgate-Palmolive Company
909 River Road
P.O. BOX 1343
Piscataway, NJ 08855-1343

FEB 25 1993

Dear Mr. Hammes:

Reference is made to the request for a waiver of *in vivo* bioequivalence requirements dated December 13, 1990 for chlorhexidine gluconate 0.12% oral rinse.

The waiver request has been reviewed by the Division of Bioequivalence and we have the following recommendations:

RECOMMENDATIONS:

The Division of Bioequivalence has concluded that Colgate-Palmolive Company has failed to demonstrate that PerioGard® (chlorhexidine gluconate, 0.12%) oral rinse meets the criteria for a waiver of the bioequivalence requirements under 21 CFR 320.22(b)(3).

Specifically, Colgate-Palmolive has not demonstrated that the proposed product "contains no inactive ingredient or other change in formulation from the drug product that is the subject of the approved full new drug application that may significantly affect absorption of the active drug ingredient or active moiety."

FDA regulations at 21 CFR 314.94(a)(9)(ii) state in pertinent part: "...an applicant shall identify and characterize the inactive ingredients in the proposed drug product and provide information demonstrating that such inactive ingredients do not affect the safety of the proposed product." FDA has concluded that unless your proposed product is **the same as the referenced**

listed product, a bioequivalence study must be performed to demonstrate that the differences do not affect the safety of the proposed product.

Therefore, you have two options:

1) reformulate your product to eliminate any differences between your proposed product and the reference listed product that may significantly affect absorption of the active drug ingredient or active moiety, or

2) perform a bioequivalence study that demonstrates that the product as proposed is bioequivalent to the reference listed drug.

Your attention is directed specifically to the concentrations and ranges for glycerin and sorbitan.

All responses and correspondence with regard to this letter should be sent to the Office of Generic Drugs, HFD-630.

Sincerely yours,

/S/ 2/25/93

Roger L. Williams, M.D.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA #
DIPS/ Division Files
HAC-130/ JAllen
HFD-600 Reading File 2/18/93
HFD-638
HFD-630

ANDA 73-695

JAN 12 1993

Colgate-Palmolive Company
Attention: Craig E. Hammes
909 River Road
Piscataway, NJ 08854-5596

Dear Sir:

This is in reference to your abbreviated new drug application dated December 13, 1990, submitted pursuant to Section 505(j) of the Food, Drug, and Cosmetic Act, for Chlorhexidine Gluconate Oral Rinse, 0.12%.

Reference is also made to your amendment dated October 13, 1992.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

1. Please provide, if applicable, certified documentation from that the drug substance is no longer designated as BP.

2. Please submit an updated certificate of analysis from for drug substance currently in use or planned for use in the manufacture of the drug product, chlorhexidine gluconate, 0.12%.

3. Please provide from Colgate-Palmolive Co. complete in-house analytical data, including comparative IR spectra and impurity profile data (impurity identity, impurity specification limits and chromatographic characterization), for the same lot of drug substance to which certificate of analysis refers. You must demonstrate confirmation of COA for the active drug ingredient.

4. If the drug substance remains designated as BP by please provide the method validation data for all specification parameters whose test methodology is altered from the BP monograph.

5. As requested below, please obtain and provide the updated information from your suppliers for the excipients listed; and, in addition, as per 21 CFR 211.84(d)(2), you must provide your own verifying in-house analytical data for all drug product ingredients, including the drug substance. In lieu of this testing, a supplier's certificate of analysis may be accepted

provided that at least one specific identity test is conducted, and provided that you have established the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate stated intervals.

Glycerin USP: Supplier must update its specification requirements to include "Organic volatile impurities" per USP XXII, Supplement 7, page 3056.

PEG 40 Sorbitan Diisostearate: Supplier must list applicable limit requirements for all the specification parameters.

Menthol USP: Supplier must update its specification requirements to conform with USP XXII monograph, page 821, and Supplement 6, page 2858.

Anethole NF: Supplier must update its specification requirements to conform with USP XXII monograph, page 1900, and Supplement 6, page 2957.

Eugenol USP: Supplier must update its specification requirements to conform with USP XXII monograph, page 557.

6. Please specifically describe in the batch records the equipment vessel's construction and volume capacity.

7. Your container/closure system usage is unclear. If the prototype bottles, used for stability studies, will be the same as that specified for future bottle manufacture, then you must clearly state and commit to this. However, if future produced bottles with the stated intended specifications are not the same as the prototype bottles, then you must commit to submit new stability data in the bottles which will be marketed.

   Please explain which case is relevant and submit the appropriate comments.

8. Giving the yield of bulk drug product is acceptable; however, batch records should also provide yield of finished product by including a batch filling reconciliation statement which clearly explains the disposition of all product. Please include a filling reconciliation statement in future batch records.

9. Please provide release specification limits, test methodology and method validation data for Related Substances in the final drug product; or, if this is

not applicable, please provide sufficient experimental data to show that testing for Related Substances in the drug product is not required.

10. In reference to Comment No. 7 in our letter to you dated May 26, 1992, your reply is interpreted that you are withdrawing the long-term stability studies as support of expiration dating for the drug product. Please confirm.

11. If the pilot-scale batches, CP9R-425/426/427, are to be used to support the expiration dating of the product, please provide the executed batch records for these pilot-scale batches, which should include certificates of analyses and product filling reconciliation data for these batches.

In addition to responding to these deficiencies, please note and acknowledge the following in your response:

12. Please be reminded to include in your stability report forms a statement listing the manufacturer of the drug substance.

13. Firms referenced in the application relative to the manufacturing and testing of the product must be in compliance with CGMPs at the time of approval. At the appropriate time, we will request an evaluation from the Division of Manufacturing and Product Quality.

14. With regard to your facsimile memorandum from P.J. Okarma dated 11/2/92, you are informed of the following:

    A change in the manufacturing process as contemplated by this memo will require submission of a formal amendment to this ANDA for pre-approval review. The amendment should include master and executed batch procedures (to include product reconciliation data), description and data for in-process control efforts, description and size of the blending tank, description and specifications of all container/closure systems used with vendor's certificate of analyses, product analytical data, and stability data of the finished product showing acceptable storage life and compatibility of the drug product with all the container/closure systems.

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 the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this

letter will be considered a major amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing. You will be notified in a separate letter whether a clinical bioequivalence study for this drug product will be required.

Sincerely yours,

/S/ 1/4/93

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

cc: ANDA #73-695
ANDA #73-695/DUP/Division File
HFC-130/JAllen
HFD-600/Reading File

Endorsements:

HFD-633/D.James/12-30-92 D. James 1/11/93

HFD-638/C.Shannon/ 1-11-93

HFD-633/P.Schwartz, Ph.D./1-4-93 PS 1/11/93

HFD-633/J.Dawson/CSO/1-4-93 JD 1-11-93

NOT APPROVABLE - Major Amendment

ANDA 73-695

Colgate-Palmolive Company
Attention: Paul J. Okarma, Ph.D.
P.O. Box 1343
909 River Road
Piscataway, NJ 08855-1343

NOV 3 1993

Dear Sir:

This is in reference to your abbreviated new drug application dated December 13, 1990, submitted pursuant to Section 505(j) of the Food, Drug, and Cosmetic Act, for Chlorhexidine Gluconate Oral Rinse, 0.12%.

Reference is also made to your amendments dated November 13 and December 4, 1992 and January 20, May 17, and August 11, 1993.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies

B. Labeling Deficiencies

1. General Comment:

On your container labels and carton labeling, your corporate logo and address is far more prominent than the manufacturer's name and address. In addition, your "Manufactured for ____ by ____ " statement does not meet a minimum of 4-point size type print. In your package insert labeling, your corporate name and address "stands alone" at the bottom center of the insert and is not qualified as required by 21 CFR 201.1(h)(2). We believe the way in which this information appears on your labels and labeling is misleading in that it suggests that the product is manufactured by Colgate-Palmolive Company.

Revise your container labels, carton, and package insert labeling so the statements identifying the manufacturer and the distributor are qualified and meet a minimum of 4-point size type print.

2. INSERT (PRECAUTIONS)

a. All subsection headings should be less prominent than your section heading.

b. Delete in the Pregnancy subsection.

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 the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MINOR amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/ 11/3/93

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

COLGATE-PALMOLIVE COMPANY

P.O. Box 1343
909 River Road
Piscataway, NJ 08855-1343

Paul J. Okarma, Ph.D.
Associate Director
Regulatory Affairs
Telephone (908) 878-7323
Telefax (908) 878-7135

January 6, 1994

Rashmikant M. Patel, Ph.D.
Director, Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855

NC
NEW CORRES

Subject: ANDA 73-695: Chlorhexidine Gluconate Oral Rinse, 0.12%

Dear Dr. Patel:

This letter is to clarify that the primary stability data on the exhibit batch for ANDA 73-695 was submitted to the agency in our submission of May 17, 1993, pages 237 through 249. The stability storage and analytical testing to generate this stability data on the exhibit batch was performed at our Canton, Massachusetts facility. This is stated in our submission of October 13, 1992, page 022.

If you have any questions, please telephone me. My direct dial number is 908-878-7323.

Respectfully,

Paul J. Okarma

Paul J. Okarma, Ph.D.
Associate Director
Regulatory Affairs

Telephone: (908) 878-7323
Telefax: (908) 878-7135

Attachments

RECEIVED
JAN 0 7 19
GENERIC DRUGS

ORIGINAL

ORIGINAL

COLGATE-PALMOLIVE COMPANY

PO Box 1343
909 River Road
Piscataway, NJ 08855-1343

Paul J. Okarma, Ph.D.
Associate Director
Regulatory and Government Affairs
Telephone (908) 878-7323
Telefax (908) 878-7135

Meeting Request Denied
See TCon 8/19/93

August 11, 1993

Roger L. Williams, M.D.
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MPN II, HFD-600
5600 Fishers Lane
Rockville, MD 20857-1706

RECEIVED
AUG 12 1993
GENERIC DRUGS

Subject: ANDA 73-695: Chlorhexidine Gluconate Oral Rinse, 0.12%
Amendment to an Unproved Application (21 CFR § 314.60)
Request for Meeting

Dear Dr. Williams:

This letter respectfully requests a meeting with you and your staff to discuss the review of our Abbreviated New Drug Application for Chlorhexidine Gluconate Oral Rinse, 0.12%, ANDA 73-695. We believe that this application is near approval, and are concerned about the length of the final stages of the review. Colgate-Palmolive expected FDA review of the final chemistry amendment to be completed in August. We now understand that it will be no sooner than October or November. The purpose of the meeting will be to also discuss the manner in which Colgate-Palmolive can assist the agency to bring review of this submission to a successful and rapid conclusion.

The original ANDA was submitted to the agency in 1990. A successful pre-approval inspection was conducted by the local district office in late 1991, and we worked with the FDA testing laboratory in early 1992 to complete methods validation. We were originally informed that this product would qualify for a bioequivalence waiver, and we believed that the bioequivalence waiver had been granted in February 1991. The bioequivalence waiver resurfaced as an item of further discussion within the agency in mid-1992, an item which was not resolved until earlier this year. Also, we have replied to two requests for additional information on the chemistry section of the application. Our replies to the second request were submitted in mid-May, and review and acceptance of this amendment is the only remaining item for approval.

For your convenience, a chronology of the major items of the three-year review is attached (Appendix 1), and will be further elaborated at our meeting. As shown by this brief summary, Colgate is committed to working constructively with the agency, has been diligent in following the course of submission review, and has promptly addressed agency comments and requests for additional information. For these reasons, we are anxious to successfully complete the review and approval of this file.

Representatives from Colgate-Palmolive that will attend the meeting are:

Hulon McCain, Ph.D. Senior Section Head, Regulatory Affairs;
Richard Theiler, Ph.D. Worldwide Director, Colgate Oral Pharmaceuticals;

and the undersigned. Proposed dates for the meeting are September 1, 3, 14, 15, 16, and 17. The earlier dates, September 1 and 3, are preferred. I will follow-up with Mr. Gordon Johnston to confirm the meeting date, time, and location.

We wish to thank you and your staff for your cooperation and assistance throughout the review. Messrs. Don Hare, Gordon Johnston, and Harvey Greenberg, have been especially helpful during this protracted review. If you have any questions, please telephone me. My direct dial number is 908-878-7323.

Respectfully,

Paul J. Okarma, Ph.D.
Associate Director
Regulatory and Government Affairs

Telephone: (908) 878-7323
Telefax: (908) 878-7135

August 11, 1993

BIOAVAILABILITY

COLGATE-PALMOLIVE COMPANY

909 River Road
Piscataway, NJ 08854-5596

Paul J. Okarma, Ph.D.
Associate Director
Regulatory and Government Affairs
Telephone (908) 878-7323
Telefax (908) 878-7135

May 17, 1992

RECEIVED
MAY 18 1993
GENERIC DRUGS

Roger L. Williams, M.D.
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MPN II, HFD-600
5600 Fishers Lane
Rockville, MD 20857-1706

Subject: ANDA 73-695: Chlorhexidine Gluconate Oral Rinse, 0.12%
Amendment to an Unproved Application (21 CFR 314.60)
Response to FDA Letter of January 12, 1993
Request for a Waiver from the Conduct of Bioequivalence Studies
Expedited Review Requested

Dear Dr. Williams:

This submission is a major amendment and presents replies to Dr. Patel's comments in his letter of January 12, 1993 on the chemistry, manufacturing and controls section of this ANDA. We have addressed each comment completely, and this submission contains replies to all outstanding information requested by the agency to complete review of this ANDA. For convenience, each comment is presented and is followed by the appropriate reply. Supporting documentation is provided as appendices.

This submission also restates our request for a waiver from the conduct of bioequivalence studies, as this request is consistent with the ANDA final rule.

Request for a waiver from the conduct of bioequivalence studies:

We reaffirm the bioequivalence waiver request that was contained in the original submission of December 1990 and was recently restated in our letters of July 20 and November 13, 1992. We agree with the Agency's original conclusion that a waiver from bioequivalence studies is warranted for this type of product, and that a waiver is consistent with the Final Rule for ANDAs. The request is based on the following:

(1) the same active ingredient, chlorhexidine gluconate, is used in both the innovator and our product,
(2) the active ingredient is formulated at the same concentration, 0.12 percent,
(3) the drug product is a solution,
(4) this is a topical drug product, and
(5) the products are the same formulation.

We recognize the difficulty in defining the criteria whereby formulations are considered to be the same. To address agency comments on this subject, we have adjusted the formulation of Colgate Periogard slightly to match the innovator's product. The revised formulation is submitted in the attached replies to comments on the chemistry information in the application and may be found in Appendix 7.

Therefore, we reaffirm our original request for a waiver from the conduct of bioequivalence studies for this product.

Request for expedited review:

We appreciate the cooperation that the Agency has consistently shown throughout the review of this submission. We also recognize the difficulties presented by: (1) Colgate's being among the first companies to request a bioequivalence waiver in the submission of an ANDA, and (2) Colgate's being among the first companies to submit an ANDA for this product.

In light of the time required to evaluate the initial requests for a bioequivalence waiver and the deliberations necessary to reach agreement throughout the Agency on the criteria whereby a bioequivalence waiver may be granted, we request expedited review of this submission.

As (1) this submission represents the second reply to Agency comments on the chemistry, manufacturing, and controls portion of the application, (2) replies to the comments addressed in this submission were straightforward, and (3) we have already received a successful pre-approval inspection in late 1991, we request that additional clarification of items contained herein be communicated by telephone to the undersigned, if additional information is required by the agency.

Finally, please note that the operating subsidiary which will market this product is now known as Colgate Oral Pharmaceuticals. This is only a name change. The sites listed in the submission for manufacturing, control, and inventory of product remain unchanged.

Since our last submission to this file, Mr. Craig Hammes, former Corporate Director of Regulatory and Government Affairs has left Colgate-Palmolive Company. Please forward any future correspondence regarding this ANDA to my attention.

We wish to thank you and your staff for your cooperation, prompt attention, and assistance throughout the review. If you require any additional information to complete agency review of this application, please telephone me.

Respectfully,

Paul J. Okarma, Ph.D.
Associate Director
Regulatory and Government Affairs

Telephone: (908) 878-7323
Telefax: (908) 878-7135

Attachment

May 17, 1993

COLGATE-PALMOLIVE COMPANY

PO. Box 1343
909 River Road
Piscataway, NJ 08855-1343

Paul J. Okarma, Ph.D.
Associate Director
Regulatory Affairs
Telephone (908) 878-7323
Telefax (908) 878-7135

November 22, 1993

Labeling Satisfactory 12/9/93 C. Kopcha

NDA DRG AMENDMENT

Rashmikant M. Patel, Ph.D.
Director, Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855

Subject: ANDA 73-695: Chlorhexidine Gluconate Oral Rinse, 0.12%
MINOR AMENDMENT
Amendment to an Unapproved Application (21 CFR § 314.60)
Replies to FDA Letter of November 3, 1993

Dear Dr. Patel:

This **MINOR AMENDMENT** provides replies to final agency comments on our Abbreviated New Drug Application for Chlorhexidine Gluconate Oral Rinse, 0.12%. We appreciate the attention and cooperation we have received from agency staff during the final months of agency review of this application, and we look forward to soon receiving approval to market this product.

Recent discussion on October 5, 1993 with Ms. Mimi Roa Remache of the Newark (West Orange) District Office indicates the district will recommend approval of this product.

If you have any questions, please telephone me. My direct dial number is 908-878-7323.

Respectfully,

Paul J. Okarma, Ph.D.
Associate Director
Regulatory Affairs

Telephone: (908) 878-7323
Telefax: (908) 878-7135

Attachments

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COLGATE-PALMOLIVE COMPANY

PO. Box 1343
909 River Road
Piscataway, NJ 08855-1343

January 20, 1993

Craig E. Hammes
Corporate Director
Regulatory and Government Affairs
Telephone (908) 878-7193
Telefax (908) 878-7135

Rashmikant M. Patel, Ph.D.
Director, Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MPN II, HFD-600
5600 Fishers Lane
Rockville, MD 20857-1706

ORIG NEW CORRES
1.21.93

Subject: ANDA 73-695; Chlorhexidine Gluconate Oral Rinse, 0.12%
Amendment to an Unapproved Application (21 CFR 314.60)
Notice of Intent to Amend Application

Dear Dr. Patel:

This letter serves as notification of our intent to amend our abbreviated new drug application for Chlorhexidine Gluconate Oral Rinse, 0.12%, as provided by 21 CFR § 314.120(a). This notification is made in reply to your letter of January 12, 1993 and is provided within ten days of receipt of your letter.

A major amendment will be submitted providing complete responses to all questions in your letter of January 12, 1993, and providing for a revised product formulation and chemistry information. The revised formulation is provided in attachment I to this letter, and is the same as that of the innovator product, Peridex® (chlorhexidine gluconate 0.12%) Oral Rinse, NDA 19-028. The amendment will renew Colgate-Palmolive's request for a waiver of *in vitro* and *in vivo* bioequivalency for the ANDA for PerioGard® (chlorhexidine gluconate 0.12%) Oral Rinse.

If you have any questions on this submission, please do not hesitate to contact me or Paul J. Okarma, Ph.D., manager, regulatory affairs.

Respectfully,

Craig E. Hammes

Craig E. Hammes
Corporate Director
Regulatory and Government Affairs

Telephone: (908) 878-7193 Telefax: (908) 878-7135
Attachment

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JAN 2 2 1993
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Vol. 3-1

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COLGATE-PALMOLIVE COMPANY

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Craig E. Hammes
Corporate Director
Regulatory and Government Affairs
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NEW CORRESP

December 4, 1992

Roger L. Williams, M.D.
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MPN II, HFD-600
5600 Fishers Lane
Rockville, MD 20857-1706

BIOAVAILABILITY MATERIAL

Subject: ANDA 73-695; Chlorhexidine Gluconate Oral Rinse, 0.12%
Bioequivalence study for ANDA 73-695 and request for a meeting

Dear Dr. Williams:

The attached letter and protocol have been concurrently submitted to our Investigational New Drug application for Chlorhexidine Gluconate Oral Rinse, 0.12% (IND The submission presents a protocol for a clinical bioequivalence study and requests agreement that this study will be accepted by the agency.

Respectfully,

Craig E. Hammes
Corporate Director
Regulatory and Government Affairs

Telephone: (908) 878-7193
Telefax: (908) 878-7135

Attachments
CEH:pjo

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DEC 04 1992
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(TITLE 21, CODE OF FEDERAL REGULATIONS, 314)

Form Approved: OMB No. 0910-0001
Expiration Date: March 31, 1990
See OMB Statement on Page 3.

FOR FDA USE ONLY

DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS.

NOTE: No application may be filed unless a completed application form has been received *(21 CFR Part 314)*.

NAME OF APPLICANT	DATE OF SUBMISSION
Colgate-Palmolive Company	December 4, 1992
ADDRESS (Number, Street, City, State and Zip Code)	TELEPHONE NO. *(Include Area Code)*
909 River Road P.O. Box 1343 Piscataway, NJ 08855-1343	(908)-878-7500 NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued) ANDA 73-695

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)*	PROPRIETARY NAME *(if any)*
Chlorhexidine Gluconate	PerioGard®Oral Rinse

CODE NAME *(if any)*	CHEMICAL NAME
None	*N, N"*-bis(4-chlorophenyl)-3,12-diimino-2,4,11,13-tetraazatetradecanediimidamide di-D-gluconate

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
Oral Rinse	Topical	0.12%

PROPOSED INDICATIONS FOR USE

For the treatment of gingivitis

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR PART 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR PART 314), AND DRUG MASTER FILES (21 CFR 314.420) REFERRED TO IN THIS APPLICATION:

INFORMATION ON APPLICATION

TYPE OF APPLICATION *(Check one)*

____THIS SUBMISSION S A FULL APPLICATION (21 CFR 314.50) __X__THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION
Peridex® (chlorhexidine gluconate 0.12%) Oral Rinse	Procter & Gamble Company, NDA 19-028

STATUS OF APPLICATION *(Check one)*

___ PRESUBMISSION __XX__ AN AMENDMENT TO A PENDING APPLICATION ___ SUPPLEMENTAL APPLICATION

___ ORIGINAL APPLICATION ___ RESUBMISSION

PROPOSED MARKETING STATUS *(Check one)*

__X__ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT (Rx) ___ APPLICATION FOR AN OVER-THE-COUNTER PRODUCT (OTC)

CONTENTS OF APPLICATION	
This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Summary (21 CFR 314.50(c))
	3. Chemistry, manufacturing and control section (21 CFR 314.50(d)(1))
	4. a. Samples (21 CFR 314.50(e)(1)) (Submit only upon FDA's request)
	b. Methods Validation Package (21 CFR 314.50(e)(2)(i))
	c. Labeling (21 CFR 314.50(e)(2)(ii))
	i. draft labeling (4 copies)
	ii. final printed labeling (12 copies)
	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50(d)(2))
X	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50(d)(3))
	7. Microbiology section (21 CFR 314.50(d)(4))
	8. Clinical data section (21 CFR 314.50(d)(5))
	9. Safety update report (21 CFR 314.50(d)(5)(vi)(b))
	10. Statistical section (21 CFR 314.50(d)(6))
	11. Case report tabulations (21 CFR 314.50(f)(1))
	12. Case reports forms (21 CFR 314.50(f)(1))
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
X	15. OTHER *(Specify)* Letter and request for a meeting.

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as follows: (1) 4 months after the initial submission, (2) following receipt of an approvable letter and (3) at other times as requested by FDA. If this application is approved, I agree to comply with all laws and regulations that apply to approved applications, including the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211.
2. Labeling regulations in 21 CFR 201.
3. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
4. Regulations on making changes in application in 21 CFR 314.70, 314.71, and 314.72.
5. Regulations on reports in 21 CFR 314.80 and 314.81.
6. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the controlled substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

NAME OF RESPONSIBLE OFFICIAL OR AGENT	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	DATE
Craig E. Hammes Corporate Director Regulatory and Government Affairs		

ADDRESS *(STREET, CITY, STATE, ZIP CODE)*	TELEPHONE NO. *(Include Area Code)*
Colgate-Palmolive Company 909 River Road P. O. Box 1343 Piscataway, NJ 08855-1343	Telephone: (908) 878-7193 Telefax: (908) 878-7135

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

COLGATE-PALMOLIVE COMPANY

P.O. Box 1343
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Craig E. Hammes
Corporate Director
Regulatory and Government Affairs
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November 13, 1992

Roger L. Williams, M.D.
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MPN II, HFD-600
5600 Fishers Lane
Rockville, MD 20857-1706

Subject: ANDA 73-695; Chlorhexidine Gluconate Oral Rinse, 0.12%
Bioequivalence study for ANDA 73-695 and request for a meeting

Dear Dr. Williams:

This submission presents a protocol for the conduct of an in vivo study to demonstrate the bioequivalence of Colgate-Palmolive's chlorhexidine-gluconate oral rinse and the innovator's product.

In light of the outstanding issues surrounding the bioequivalence waiver for our abbreviated new drug application for a chlorhexidine gluconate oral rinse, we request a meeting with the agency at the earliest possible date. Proposed dates for this meeting are any day between December 7 and 21, 1992. At this meeting we will request agency agreement on the study required to demonstrate bioequivalence.

We propose to conduct a three-week in vivo bioequivalence study. This study incorporates a clinical endpoint, as requested by Dr. Chambers. A rationale for the use of the three-week experimental gingivitis model is submitted in Attachment 1, and a draft clinical protocol is submitted in Attachment 2.

We continue to believe that both (1) a waiver from the conduct of bioequivalence studies for this product is consistent with the Final Rule for ANDAs, and (2) if required, meaningful bioequivalence data for this product can be gathered with the conduct of the short-term human study, supported by in vitro data, following the protocols submitted to the agency under this ANDA on October 12, 1992. However, we wish to meet and review the attached bioequivalence protocol to move the submission review to completion. Neither this submission, nor the conduct of the attached bioequivalence study, represent an agreement that this study is the preferred means whereby bioequivalence may be demonstrated for products of this type.

As you know, our original application contained a request for a waiver from the determination of bioequivalence, as suggested by Dr. Ise prior to his retirement from the agency. Dr. Ise informed us on October 23, 1990, prior to submission of the ANDA, that the agency had met to discuss this product, and a waiver from the determination was warranted, provided agency review of the submission concluded that the formulations were equivalent.

In a recent letter to you, dated July 20, 1992, we reaffirmed our request for the bioequivalence waiver. We strongly agree with the agency's original conclusion that a waiver from bioequivalence studies is warranted for this type of product, and a waiver is consistent with the Final Rule for ANDAs. The request for a waiver is based on the following: (1) the same active ingredient, chlorhexidine gluconate, is used in both the innovator and our product, (2) the active ingredient is formulated at the same concentration, 0.12 percent, (3) the drug product is a solution, (4) this is a topical drug product, and (5) the products are the same formulation.

Additionally, a waiver is consistent with agency policy regarding a waiver from submission of bioavailability data in NDAs for chlorhexidine gluconate-containing oral rinses. For example, Dr. Palmer, then acting director, Division of Radiopharmaceutical, Surgical and Dental Products, concluded the following, upon review of our NDA for a chlorhexidine gluconate oral rinse, NDA

> "Our Division of Biopharmaceutics has reviewed your request for a waiver of in vivo bioavailability studies and has concluded that bioavailability is not necessary for the product to achieve its intended purpose because: (1) the drug product is intended for local therapeutic effect (in the mouth); and (2) it is not intended to be absorbed. Furthermore, the proposed labeling indicates that the usual dose will be two undiluted 15 ml doses per day which will be swished around the mouth and then expectorated. The Division of Biopharmaceutics, therefore, recommends that a waiver of in vivo biopharmaceutics studies be granted according to the provisions of 21 CFR 320.22(b)(2) and (3)." [Letter, John F. Palmer, M.D. to Colgate-Palmolive Company, July 28, 1989]

In conclusion, we believe that a waiver is warranted and request a bioequivalence waiver. However, we appreciate the issues the waiver has raised at the agency. In the interest of moving agency review of the submission to completion, we are willing to conduct a bioequivalence study with a clinical endpoint, as requested by the agency.

We would like to meet with the agency at your earliest convenience to discuss the enclosed study protocol and the criteria which must be met to demonstrate bioequivalence for a chlorhexidine gluconate-containing oral rinse. Representatives from Colgate-Palmolive Company that will attend the meeting are Dr. K. Klimpel, research associate, professional products, Dr. P. Okarma,

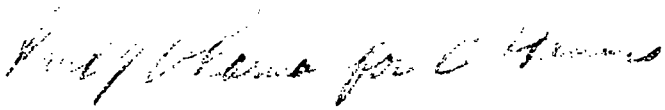
manager, regulatory affairs, Dr. R. Theiler, worldwide director, professional products, and the undersigned. As previously stated, proposed dates are December 7 through the 21.

Dr. Okarma will follow-up to schedule the meeting. His telephone number is 908-878-7323.

As always, we appreciate your continued assistance to resolve this issue and will work closely with your staff to set a firm date at the earliest mutually convenient time.

This submission has also been filed to our IND for chlorhexidine gluconate oral rinse, IND

Respectfully,



Craig E. Hammes
Corporate Director
Regulatory and Government Affairs

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Attachments
CEH:pjo

Orig

COLGATE-PALMOLIVE COMPANY

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FPL: Container labels, Carton, Package Insert Labeling Satisfactory. See Worksheet Review 12-22-92

NDA ORIG AMENDMENT

October 13, 1992

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OCT 1 3 1992

GENERIC DRUGS

Rashmikant M. Patel, Ph.D.
Director, Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MPN II, HFD-600
5600 Fishers Lane
Rockville, MD 20857-1706

Subject: ANDA 73-695; Chlorhexidine Gluconate Oral Rinse, 0.12%
Amendment to an Unapproved Application (21 CFR 314.60)
Reply to FDA Letter of May 26, 1992

Dear Dr. Patel:

This submission presents replies to the comments in your letter of May 26, 1992 on our application for Chlorhexidine Gluconate Oral Rinse, 0.12%. As requested in your letter, all comments are addressed in their entirety. We believe that we have satisfactorily addressed all FDA comments raised in your letter of May 26 on the chemistry, manufacturing, and controls and the labeling sections of the application.

If you have any questions on this submission, please do not hesitate to contact Paul J. Okarma, Ph.D., manager, regulatory affairs. His telephone number is (908) 878-7323, and he can be reached by telefax at (908) 878-7135.

Respectfully,

Paul J. Okarma for C. Hammes

Craig E. Hammes
Corporate Director
Regulatory and Government Affairs

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Attachment
CEH:ddm

COLGATE-PALMOLIVE COMPANY

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Craig E. Hammes
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October 12, 1992

Roger L. Williams, M.D.
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MPN II, HFD-600
5600 Fishers Lane
Rockville, MD 20857-1706

Subject: ANDA 73-695; Chlorhexidine Gluconate Oral Rinse, 0.12%. Bioequivalence

Dear Dr. Williams:

In light of the issues surrounding the bioequivalence waiver for abbreviated new drug applications for chlorhexidine-gluconate oral rinses, we would like to meet with the agency at your earliest convenience. As you may recall, our original ANDA submission contained a request for a waiver from the determination of in vivo bioequivalence. This request for a waiver was discussed with Dr. Ise prior to submission of the original application in December 1990.

In a recent letter to you, dated July 20, 1992, we reaffirmed our request for the bioequivalence waiver, as the waiver is consistent with the final rule for abbreviated new drug applications. Though we believe that a waiver is warranted and request a bioequivalence waiver, we appreciate the issues the waiver has raised at the agency. In the interest of moving agency review of the submission to completion, we are willing to conduct studies which are designed to demonstrate that our proposed product is equivalent to the innovator's product. We believe that a combination of (1) a short-term human clinical study, supported by (2) in vitro antimicrobial activity data would be sufficient to demonstrate equivalence between these two products.

Therefore, we have attached a draft protocol for a human clinical study (Attachment 1). The study we propose is a one-week, non-brushing, plaque-growth study, involving 48 subjects. We have also attached a copy of the laboratory procedure which will be followed to demonstrate equivalent antimicrobial activity between the two products (Attachment 2).

In conclusion, we would like to meet with the agency at your earliest convenience to discuss the enclosed study protocols and the criteria which must be met to demonstrate bioequivalence for chlorhexidine gluconate-

containing oral rinses. Representatives from Colgate-Palmolive Company that will attend the meeting are Dr. K. Klimpel, research associate, professional products, Dr. P. Okarma, manager, regulatory affairs, Dr. R. Theiler, worldwide director, professional products, and the undersigned. Proposed dates are October 19, and 20 and November 10, 11, 12, and 13.

Dr. Okarma will follow-up to schedule the meeting. His telephone number is 908-878-7323.

As always, we appreciate your continued assistance to resolve this issue and will work closely with your staff to set a firm date at the earliest mutually convenient time.

Respectfully,

Craig E. Hammes
Corporate Director
Regulatory and Government Affairs

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Attachments
CEH:pjo

ORIGINAL

COLGATE-PALMOLIVE COMPANY

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RECEIVED
JUL 2 1 1992
GENERIC DRUGS

NEW CORRESP

July 20, 1992

Roger L. Williams, M.D.
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MPN II, HFD-600
5600 Fishers Lane
Rockville, MD 20857-1706

Subject: ANDA 73-695; Chlorhexidine Gluconate Oral Rinse, 0.12%
Amendment to an Unapproved Application (21 CFR 314.60)
Reply to FDA Letter of May 26, 1992

Dear Dr. Williams:

We have received Dr. Patel's letter on the chemistry, manufacturing, and controls and labeling review of our original ANDA for Chlorhexidine Gluconate Oral Rinse, 0.12%, dated May 26, 1992. We are currently preparing a submission to address Dr. Patel's comments. This letter serves as notice of our intent to amend the original application to provide for the requested information.

As the original ANDA was submitted to the agency on December 13, 1990, and the first review letter on the application was received in late May 1992, we are anxious to work with the agency to move the review of the submission to completion.

As you know, our original application contained a request for a waiver from the determination of bioequivalence for this product, as suggested by Dr. Ise prior to his retirement from the agency. Dr. Ise informed us on October 23, 1990, prior to submission of the ANDA, that the agency had met to discuss this product, and he believed that a waiver from the determination was warranted, provided that FDA review of the submission concluded that the formulations were equivalent. Unfortunately, Dr. Ise subsequently retired from the agency.

Last year, during routine follow-up with the agency on the status of the review of the application, it was mentioned that the bioequivalence review had been completed in February 1991, and that no letter on the bioequivalence section would be issued to Colgate. We interpreted this as a grant of our bioequivalence waiver. In mid-1992, we were informed that the bioequivalence waiver for this product had now become an item of further discussion within the agency.

Colgate-Palmolive Company
Chlorhexidine Gluconate Oral Rinse, 0.12%
ANDA 73-695

We strongly agree with the agency's original conclusion that a waiver from bioequivalence studies is warranted for this type of product, and granting a waiver would be consistent with the Final Rule on ANDA submissions recently published in the *Federal Register*. The request for a waiver is based on the following: (1) the same active ingredient, chlorhexidine gluconate, is used in both the innovator and our product, (2) the active ingredient is formulated at the same concentration, 0.12 percent, (3) the drug product is a solution, (4) this is a topical drug product, and (5) the products are the same formulation. Accordingly, we request that the FDA grant the bioequivalence waiver.

We recognize that this submission is the first abbreviated application for an oral rinse formulation of chlorhexidine gluconate. If there is any additional information which Colgate-Palmolive Company can supply to assist FDA's review of the application, please do not hesitate to contact me. As previously stated, we would like to work with the agency to bring this matter to a successful and rapid conclusion.

Respectfully,

Paul J. Thoma for C. Hammes

Craig E. Hammes
Corporate Director
Regulatory and Government Affairs

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CEH:pjo

21

COLGATE-PALMOLIVE COMPANY

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Craig E. Hammes
Corporate Director
Regulatory and Government Affairs
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SUBMITTED TO FDA
MAR 25 1992

March 24, 1992

Roger L. Williams, M.D.
Director, Office of Generic Drugs
CDER, Food and Drug Administration
MPN II, HFD-600
5600 Fishers Lane
Rockville, MD 20857-1706

NDA ORIG AMENDMENT
N/A

Subject: ANDA 73-695
PerioGard® (chlorhexidine gluconate 0.12%) Oral Rinse
Amendment to an Unapproved Application (21 CFR 314.60)
Reply to FDA Pre-Approval Inspection

Dear Dr. Williams:

We have recently received a letter from Ms. Diana Kolaitis, Director, Compliance Branch, Newark District Office, requesting additional information with regard to the pre-approval inspection for ANDA 73-695 for PerioGard® (chlorhexidine gluconate 0.12%) Oral Rinse.

Attached is a copy of our reply to Ms. Kolaitis, responding to the additional comments from the pre-approval inspection, along with an appropriately revised batch record for the manufacture of the drug product.

If you have any questions, please do not hesitate to contact me.

Respectfully,

Craig E. Hammes

Craig E. Hammes
Corporate Director
Regulatory and Government Affairs

Telephone: (908) 878-7193
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Attachment
CEH:pjo

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MAR 2 6 1992
GENERIC DRUGS

COLGATE-PALMOLIVE COMPANY

909 River Road
Piscataway, NJ 08854-5596

November 25, 1991

Roger L. Williams, M.D.
Director, Office of Generic Drugs
CDER, FDA
MPN II, HFD-600
5600 Fishers Lane
Rockville, MD 20857-1706

NEW CORRESP

SUBMITTED TO FDA
NOV 25 1991

Subject: ANDA 73-695
PerioGard® (chlorhexidine gluconate 0.12%) Oral Rinse
Submission Serial Number 002
Amendment to an Unapproved Application (21 CFR 314.60)
Reply to FDA Pre-Approval Inspection

Dear Dr. Williams:

We have recently received a pre-approval inspection in connection with our ANDA 73-695 for PerioGard® (chlorhexidine gluconate 0.12%) Oral Rinse. After the completion of the inspection, we were pleased to hear that Ms. Kathleen P. Clark, FDA investigator from the Newark, NJ District Office, will recommend approval, based upon satisfactory response to her observations during the inspection.

Attached is a copy of our reply to Mr. Matthew Lewis, District Director, responding to the questions raised in the pre-approval inspection, along with an appropriately revised batch record for the manufacture of the product.

If you have any questions, please do not hesitate to contact me.

Respectfully,

Craig E. Hammes
Corporate Director
Regulatory and Government Affairs

Telephone: (908) 878-7193
Telefax: (908) 878-7135

Attachment
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NOV 26 1991
GENERIC DRUGS

ORIGINAL

COLGATE-PALMOLIVE COMPANY

909 River Road
Piscataway, NJ 08854-5596

November 25, 1991

Matthew Lewis
District Director, Mid-Atlantic Region
Food and Drug Administration
61 Main Street
West Orange, NJ 07052

Subject: ANDA 73-695
PerioGard® (chlorhexidine gluconate 0.12%) Oral Rinse
Reply to FDA Pre-Approval Inspection

Dear Mr. Lewis:

We have recently received a pre-approval inspection in connection with our ANDA 73-695 for PerioGard® (chlorhexidine gluconate 0.12%) Oral Rinse. We are pleased to hear that Ms. Kathleen P. Clark, FDA investigator from the Newark, NJ District Office, will recommend approval, based upon satisfactory response to her observations during the inspection. The following is our reply to the pre-approval inspection:

1. *FDA Comment: The master batch record does not include a provision for the adjustment of the amount of chlorhexidine gluconate added when the concentration is above/below 20% w/v. For example, chlorhexidine gluconate lot #1419, used in the manufacture of validation lot #82261, had a concentration of % w/v. The amount of active was adjusted to compensate for this difference, but the amount of active added was not adjusted in lots #03091, 03092, and 03093. Chlorhexidine gluconate lot #1630, used in the manufacture of these three lots, also had a concentration of %.*

Post-approval, the amount of drug substance, chlorhexidine gluconate BP, will not be adjusted during manufacture of the drug product to compensate for variability in Assay. The amount was adjusted in the batch mentioned above, in error, at the suggestion of the contract manufacturer, and this is not routine practice.

2. *FDA Comment: No operating parameters were stated for the mixers or for the tanks used during the manufacture of chlorhexidine gluconate 0.12% oral rinse in the master batch record or in the validation protocol or report. For example, the master batch record does not specify mixing speeds or sizes of suitable tanks.*

As discussed with Ms. Kathleen Clark during the inspection, the stirrer speed is self-regulating, as the drug product contains added surfactant. A prohibitive amount of foaming occurs if the stirrer speed is too high. We have manufactured additional batches of a placebo (surfactant) solution to enable us

to specify a stirrer speed. A revised batch record, with both the stirrer speed and tanks specified, is attached. We agree to validate the manufacturing process for the drug product, post approval, and submit this validation data to FDA for review.

We feel that we have satisfactorily addressed the comments raised during the FDA pre-approval inspection. As this reply represents a revision to the batch record for the manufacture of the drug product, this information has also been filed to ANDA 73-695.

If you have any further questions, please do not hesitate to contact me.

Respectfully,

Craig E. Hammes
Corporate Director
Regulatory and Government Affairs

Telephone: (908) 878-7193
Telefax: (908) 878-7135

Attachment
CEH:pjo

Dup. to Bio

acceptable upon initial review
John Dawson 1-16-91

COLGATE-PALMOLIVE COMPANY
909 River Road
Piscataway, NJ 08854-5596

1-19-91

December 13, 1990

Roger L. Williams, M.D.
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MPN II, HFD-600
5600 Fishers Lane
Rockville, MD 20857-1706

Re: Abbreviated New Drug Application
PerioGard® (chlorhexidine gluconate 0.12%) Oral Rinse
Submission Serial Number 000

Dear Dr. Williams:

Colgate-Palmolive Company is filing an Abbreviated New Drug Application (ANDA) for PerioGard® (chlorhexidine gluconate 0.12%) Oral Rinse. This submission follows the format proposed in the Proposed Rule for ANDAs (*Federal Register*, July 10, 1989, 28872-28942).

We are requesting a waiver for the determination of in vitro and in vivo bioequivalence for the ANDA, as discussed with Dr. Charles Ise. The approved product is Proctor & Gamble's Peridex® (chlorhexidine gluconate 0.12%) Oral Rinse.

If you have any questions, please do not hesitate to contact me

Respectfully,

Craig E. Hammes

Craig E. Hammes
Corporate Director
Regulatory and Government Affairs

Tel: (908) 878-7193
Fax: (908) 878-7135

7500

Attachment
CEH:tag