CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

73695

ADMINISTRATIVE DOCUMENTS

AUG 22 1991

REVIEW OF PROFESSIONAL LABELING

ANDA

DRAFT - Container Labels and Package Insert Labeling

DATE OF REVIEW: July 8, 1991

ANDA #: 73-695

NAME OF FIRM: Colgate Palmolive Company

NAME OF DRUG: Trade: PerioGard®
Generic: Chlorhexidine Gluconate Oral Rinse, 0.12%

DATE OF SUBMISSION: December 13, 1990

COMMENTS:

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)

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 and

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 rinses- plural)

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)

RECOMMENDATIONS:

1. Inform the firm of the above comments.

2. Request the firm revise their labels and labeling, then prepare and submit draft copies of insert labeling and final printed container labels.

3. FOR THE RECORD

a. This review is based on the labeling for PERIDEX, revised September 1987, (approved March 31, 1988) with minor modification.

b. manufactures the drug for Colgate Palmolive (the ANDA holder).

c. Dr. Ise has given a verbal okay for the bioequivalency waiver. However, the Division of Bioequivilency is contacting the Division of Medical Imaging, Surgical and Dental Drug Products on the need to perform bioequivalency studies. Our particular concerns are:

M E M O R A N D U M

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

DATE: 4/3/92

FROM: John Dawson, CSO, Central Review Branch, Office of Generic Drugs; HFD-632

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

TO: The file

SUMMARY: I spoke with Agnes Wu regarding the subject application. She informed me that she spoke with Dr. Dighe and they both agreed that the two formulations are essentially identical and that therefore the waiver of the in vivo bioequivalence study for the test product is granted as stated in the Bio Review dated 2/13/91.

/S/
John Dawson

RECORD OF TELEPHONE CONVERSATION/MEETING

DATE
1/22/92

NDA NUMBER
73695

IND NUMBER

TELECON/MEETING

INITIATED BY
- ☐ APPLICANT/SPONSOR
- ☒ FDA

MADE
- ☐ BY TELEPHONE
- ☐ IN PERSON

PRODUCT NAME
Periogard
Chlorhexidine gluconate

FIRM NAME
Colgate Palmolive

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Paul Okurma

TELEPHONE NO.

Paul Schwartz was called by Lee Alexander, of the Cincinnati FDA office who is doing methods validation for this product. He needed the BPCRS chlorhexidine impurity reference standard to complete his validation. Dr Schwartz called the firm, Mr Okurma returned his call today.

Dr Schwartz told Mr Okurma of the need for the referenced standard. Mr Okurma was to call their supplier, and would then contact Mr. Alexander. Mr Okurma also informed Dr. Schwartz they that they had already had their pre approval injection and had responded to 483. He said that they sent an amendment with a revised manufacturing formula in November 1991 as a response to 483 observation. I told him that we have no record of receiving this amendment. He was going to look into it.

SIGNATURE
/S/

DIVISION
DOE I, Branch IV

FORM FD 2587 (11/77)

DIVISION FILE

U. S. GOVERNMENT PRINTING OFFICE: 1984-477-974/C

Memorandum of Telephone Conversation

Between: John H. Dawson, Consumer Safety Officer, Review Support Branch, Office of Generic Drugs, (HFD-632)

And: Paul Karma of Colgate Palmolive Co.

Date: 9/16/91

Subject: ANDA 73-695 Chlorhexidine Gluconate Oral Rinse,

Summary: Paul Karma told me that the address for the plant site for the NDS is:

John Dawson

/S/

FOR THE RECORD

March 11, 1992

RE: Chlorhexidine Gluconate (0.12%) Oral Rinse

The labeling of the listed drug [PERIDEX; Procter & Gamble] currently states:

1) ...approximately 30% of the active ingredient is retained in the oral cavity following rinsing.

2) ...can cause staining of oral surfaces, such as tooth surfaces,...

The labeling issue is: are these statements product specific and should (or should not) be included in the generics labeling without a bioequivalence review.

K. Johnson, T. Poux, R. Pollock, K. Shah, and C. Shannon discussed whether to send out labeling comments pending the decision of a waiver of bioequivalence studies.

Upon discussion, it was decided that labeling comments should be sent out, with the clarification:

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

Cathy Shannon

/S/ 3/11/92

Copy in 73-695 (1.1)

3/11/92

RECORD OF TELEPHONE CONVERSATION/MEETING

DATE: 1/27/93

NDA NUMBER: 73-695

IND NUMBER:

TELECON/MEETING

INITIATED BY: [X] APPLICANT/SPONSOR [ ] FDA

MADE: [ ] BY TELEPHONE [ ] IN PERSON

PRODUCT NAME: Chlorhexidine Gluconate

FIRM NAME: Colgate-Palmolive

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD: Hugh McCain

TELEPHONE NO.: 908-878-7143

Mr. McCain asked about USP APE (preservative effectiveness) noting that for this product the active is the preservative. Do they need to run APE test at 3rd month accelerated station.

Stated no. Only need test for initial and commitment to run initial + expiry for 1st three market batches.

SIGNATURE: /S/ 1/27/93 Washko OSD

DIVISION: HFD-634

FORM FD 2587 (11/77)

DIVISION FILE

U. S. GOVERNMENT PRINTING OFFICE - 1984-432-976/7126

Memorandum of Telephone Conversation

Between: PS 11/3/92

Paul Schwartz, Ph.D., Supervisory Chemist, Branch IV (HFD-630)

Daniel James, Ph.D. Branch IV Chemist (HFD-630) D.J. 10/3/92

John H. Dawson, Consumer Safety Officer, Chemistry Branch IV, Office of Generic Drugs, (HFD-630)

And: Diane McPherson of Colgate-Palmolive Company

Date: November 2, 1992

Subject: ANDA 73-695 Chlorhexidine Gluconate Oral Rinse, 0.12% by Colgate-Palmolive Co.

Summary: On 11/2/92, Ms. McPherson sent to us some questions which the firm had regarding the above referenced ANDA. In our phone conversation with Ms. McPherson we discussed the following:

1. Regarding an increase in batch size, we indicated to her that our % rule would apply in this situation and they would need a test batch size of pounds.

2. A limit of 7 days maximum hold time would be needed for the blending of different batches. We would need additional information on the intermediate tank, blending time and sampling plan.

3. We would need specifications for a new container closure system, including COA from the manufacturer. DMF references should be provided. The new container closure system should be shown to be compatible with the product. We told Ms. McPherson that only one test batch would be required for review of the application.

4. We explained to Ms. McPherson that at this time we were uncertain as to whether or not a bio study would be required for this drug product.

5. Regarding equipment cleaning, we stated that this would be a matter for the district to resolve.

6. Regarding another EER, we told the firm that a pre-approval inspection would be requested near the completion of our review, but that the decission to make another at site inspection was up to the District Office.

7. Regarding the validation of the related substances test procedure, we indicated that the firm should obtain comparative results to those obtained using the British Pharmacopeia procedure.

/S/

John Dawson

NADMF

John Dawson
HFD-632

OCT 4 1991

TO: Director, Newark District, HFR-MA300

FROM: Acting Chief
Investigations & Compliance Evaluation Branch, HFD-324

SUBJ: Inspection Request
73-695
Chlorhexidine Gluconate
Oral Rinse, 0.12%

Applicant:
Colgate Palmolive Co.
909 River Road
Piscataway, NJ 08854

PROFILE: LIQ

Establishment:

CFN#: 2242829

In connection with FDA's review of ANDA 73-695, please conduct a CGMP inspection of the referenced establishment. The application provides for this establishment to manufacture, package, and test the drug product Chlorhexidine Gluconate, Oral Rinse, 0.12%. This is a Top 200 Drug Product, requiring a product specific inspection regardless of the last GMP EI covering the profile class LIQ. For guidance, refer to CP 7346.832, Pre-Approval Inspections.

This application cannot be acted upon until the inspection is completed and your findings are reported to this office. Please call well in advance if you are unable to meet the time frame, whether due to priorities or the lack of readiness on the part of the firm.

Upon completion of this assignment, please provide this office with a copy of the EIR endorsement (FDA 481(E)-(CG)). If this inspection is classified OAI, include a recommendation to withhold application approval and full documentation of CGMP violations. If the district expects delays in completing a non-violative EIR, notify this office of the inspection findings by EMS.

In communicating with this office (FTS 295-8098), reference should be made to the above ANDA number. Please direct your written response to the Compliance Evaluation Staff, HFD-320.

/S/

for/ Michael F. Karpers

Priority: ANDA Pending
Target Completion: NOV 15 1991

RECORD OF TELEPHONE CONVERSATION/MEETING

DATE: 9 March 93

NDA NUMBER: 73-695

IND NUMBER:

TELECON/MEETING

INITIATED BY: ☒ APPLICANT/SPONSOR ☐ FDA

MADE: ☐ BY TELEPHONE ☐ IN PERSON

PRODUCT NAME: Chlorhexidine Oral Rinse

FIRM NAME: Colgate Palmolive

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD: Mr. Okarma

TELEPHONE NO.:

Mr. Okarma called to inquire if it would be acceptable for the firm to manufacture the drug product for process validation.

This question was referred to Mike Smela, for comment.

Process validation is performed by the field offices ~~and it is the~~ prior to shipment of the drug product. The decision to manufacture prior to approval is the firm's decision.

This information was communicated to Mr. Okarma

SIGNATURE: /S/ CSO

DIVISION: OGD

FORM FD 2587 (11/77)

ORIGINAL IND/NDA

U. S. GOVERNMENT PRINTING OFFICE-1984-432-976/7126

RECORD OF TELEPHONE CONVERSATION/MEETING

DATE: 2/4/93

NDA NUMBER: 73-695

IND NUMBER:

TELECON/MEETING

INITIATED BY: [X] APPLICANT/SPONSOR [ ] FDA

MADE: [ ] BY TELEPHONE [ ] IN PERSON

PRODUCT NAME: Chlorhexidine Gluconate Oral Rinse

FIRM NAME: Colgate-Palmolive

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD: Hugh McCain - Colgate
R. Trumner - FDA

TELEPHONE NO.: 908-878-7143

Mr. McCain phoned re clarification of Item 3 of NA letter dated 1/12/93 re NDS impurities: We advised:

① He was correct that question was addressing issue of vendor validation. Applicant may propose reduced testing if vendor validation data (i.e. 3 lots) provided up front. Otherwise, we request they perform full testing and may supplement to reduce when data available.

Also advised that since drug is BP not USP... it should comply with BP unless fully justified why not. Analytical methods should be demonstrated as comparable.

SIGNATURE: /S/ 2-4-93 /S/

DIVISION: HFD-634

FORM FD 2587 (11/77)

DIVISION FILE

U. S. GOVERNMENT PRINTING OFFICE-1984-432-976/7126

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

The recommendations of the clinical protocol review completed February 26, 1993 by HFD-160 will not be transmitted to the firm. Colgate advised OGD that they plan to reformulate their product to match the innovator's formulation avoiding a costly clinical study. Previously the firm had been informed prior to the February 25, 1993 letter from the Division of Bioequivalence denying the waiver request. Therefore there is no need to prepare a letter to the firm

Harvey Greenberg
3/11/93

3/11/93 /S/

REVIEW OF PROFESSIONAL LABELING

Original Amendment

FPL

DATE OF REVIEW: June 7, 1993

ANDA #: 73-695

NAME OF FIRM: Colgate-Palmolive

NAME OF DRUG:
Trade: PerioGard®
Generic: Chlorhexidine Gluconate Oral Rinse 0.12%
16 fl oz

DATE OF SUBMISSION: May 17, 1993

COMMENTS:

CONTAINER, CARTON, and INSERT

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 CRF 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.

RECOMMENDATIONS:

1. Inform the firm of the above comments.

FOR THE RECORD:

1. This review was based upon the labeling of PERIDEX® (Procter & Gamble, Revised 9/87; Approved 3/31/88).

2. Container:

   i) In this submission, the firm has changed container size from 18 fl oz to **16 fl oz.**

   ii) Container is amber plastic bottle, as is the innovators.

   iii) Container closure is a child-resistant cap which does NOT function as the dosage measuring device. The firm is supplying a separate dosage measuring cup which has one fill line at 15 mL [page 226 of this submission]. This is different from the innovator, however it is satisfactory.

3. The firm has revised its product formulation. The alcohol content of the firm's product is % v/v of absolute alcohol based upon information on page 340 of this submission, calculated as follows:

4. The firm has changed the name of their marketing company for this product from:

   Colgate Hoyt/Gel-Kam
   Division of Colgate-Palmolive

   to:

   Colgate Oral Pharmaceuticals
   Subsidiary of Colgate-Palmolive

   Labels and labeling have been revised to reflect this change.

Cathy Shannon |S| 6-9-93

cc: HFD-638/CShannon/JPhillips (no cc)
mpd/6/9/93/73695.JUN
Review
Final

|S| 6/10/93

RECORD OF TELEPHONE CONVERSATION/MEETING

DATE
6-21-93

NDA NUMBER
73-695

IND NUMBER

TELECON/MEETING

INITIATED BY
- [x] APPLICANT/SPONSOR
- [ ] FDA

MADE
- [ ] BY TELEPHONE
- [ ] IN PERSON

PRODUCT NAME
Chlorhexidine Gluconate Oral Rinse

FIRM NAME
Colgate Palmolive

NAME AND TITLE OF PERSON WITH
Paul Okarma
Assoc Director
Reg Affairs

TELEPHONE NO.
908-878-7323

OGD Personnel
Gordon Johnston
Harvey Greenberg

The firm requested a telecon to discuss the status of this ANDA based on a referral from Don Hare. Mr. Okarma provided a chronology of submissions / FDA responses / bio questions. The firm is distressed that approval is taking so long (originally submitted 12/90). He asked if expedited review is a possibility. I review the policy for expedited review + noted that it applied to supplements only. We discussed OGD policy on 1ST in - 1ST received + minor amendments. Mr Okarma was advised that OGD does not expedite review of ANDAs in such cases. We also discussed telephone amendments + minor amendment definitions.

I agreed to try to give the firm a target date for chemistry review. Harvey will make sure that the waiver request is in the bio queue.

SIGNATURE
/S/

DIVISION

HFD-287 (11/77)

ORIGINAL IND/NDA

Record of Telephone Conversation

July 21, 1993

Subject: Status of 73-695 (Chlorhexidine Gluconate Oral Rinse) and 74-154 (Sodium Monofluorophosphate Dental Gel)

Contact: Paul Okarma /Colgate Palmolive (908-878-7323)

I called the firm back to update the status of the two above ANDAs. The firm was rechecking the status from an earlier telephone conversation. Regarding the Chlorhexidine Gluconate, I told the firm that the Division of Bioequivalence had completed their review and that he would not receive a letter granting the bio waiver. The application is still pending chemistry review, has been inhouse about two months and estimated another two months before completion. He will call back in about one to two months for another status check. Regarding the dental gel, the ANDA is pending consult from HFD-160. The firm has concerns about conducting a rat caries study which is part of a final Dental OTC monograph. The firm did not do a rat caries study as part of their ANDA submission. I will follow-up the consult and try to resolve the rat caries issue, if possible. I had no time table for publication of the OTC monograph.

Harvey Greenberg
7/22/93

Record of Telephone Conversation

July 28, 1993

Subject: "The continuing" status of ANDA 73-695 Chlorhexidine Gluconate Oral Rinse

Contact: Paul Okarma / Colgate Palmolive (908-878-7323)

After talking with Gordon Johnson and Mike Smela, I called the firm back to again update the status of ANDA 73-695. Referring to our July 21, 1993 conversation, I thought that the review que might be around four months. This is true in many cases however, the que for this ANDA is longer and closer to six months. The purpose of the phone call was to correct any impression that the review would be completed early (around four months).

The firm believes that they are getting the run around because the ANDA switched branches. I explained the switch was part of the random assignment switch and that hundreds of applications changed chemists. He did not seem to care and complained that OGD had this application for three years. He complained that initially (1990) a bio waiver was going to be granted and that we changed our policy over time regarding the waiver causing delay of approval. I told him that I cannot go back in time. I explained that it was the firms' right to request a meeting, however, I could not guaranteed a meeting. He would need to request a meeting in writing to the Officer director, which he said the firm would do. He was upset and I am sure that I would hear from him again.

Harvey Greenberg HG 7/29/93
7/29/93

ANDA 73045

RECORD OF TELEPHONE CONVERSATION

DATE: 8 December 1993

PRODUCT NAME: Chlorhexidine Gluconate

DMF NUMBER: 3003

FIRM NAME: Zeneca (formerly ICI)

NAME OF PERSON WITH WHOM CONVERSATION WAS HELD: Stephen Thomas

PARTICIPANT(S) TELEPHONE: (302) 886-3000

MINUTES OF CONVERSATION:

A phone inquiry was made to Mr. Thomas to clarify the location for manufacture of the drug substance.

He stated that the Chlorhexidine Base was manufactured at the
This product was shipped to the to prepare the 20% solution.

NAME OF OGD REPRESENTATIVE: Valerie Vashio, CSC /S/ 12/8/93

DIVISION/BRANCH: Div Chem I/Branch 2

1223

MEMO OF TELCON

DATE: Ncvember 8, 1993

BETWEEN: Paul Okarma/Colgate (908-878-7323)

SUBJECT: ANDA 73-695 Chlorhexidine Gluconate Oral Rinse

I had a phone call regarding the status of their chemistry NA letter. The firm believed the letter would be issued last week and Paul Okarma told me that the branch would fax the letter when completed. I did not check further since the letter was issued 11/3/93 and faxed them a copy (11/8/93).

Harvey Greenberg

11/8/93

RECORD OF TELEPHONE CONVERSATION

DATE: November 11, 1993

PRODUCT NAME: Chlorhexidine Gluconate Oral Rinse, 0.12%

ANDA/AADA NUMBER: 73-695

FIRM NAME: Colgate Palmolive Inc.
Piscataway, NJ

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD: Ms. Diane McPherson
Mr. Ken Klimpel

PARTICIPANT(S) TELEPHONE: (908)-878-7933

MINUTES OF CONVERSATION:

Discussion involved around Questions 1 and 4 from our letter of November 3, 1993.

Question 1:

The chemist wanted to know if they could photocopy the IR reference spectra of Chlorhexidine found on page 819 of Vol. 1 of the BP 1988. I told him that since these spectras are reference spectras, a photocopy of this spectra would be satisfactory to submit into the application.

Question 4:

The firm is willing to commit themselves to provide this information with their production batches and set standards accordingly. CP will revise their stability protocol to meet this commitment. I informed them that they should provide this information for batch 22617 at their next test station at room temperature so we could review the analytical method with real data. Mr. Klimplel agreed to submit data of the drug product at the 12 month station, then annually for impurities and include individual limits and specifications.

At this point the conversation ended.

NAME OF OGD REPRESENTATIVE: /S/ 11/22/93

Ms. Valerie Vashio Mr. Stephen Sherken /S/ 11/24/93

SIGNATURE OF OGD REPRESENTATIVE:

DIVISION/BRANCH: Division of Chemistry I/ Branch II/ HFD-625

RECORD OF TELEPHONE CONVERSATION

DATE: August 19, 1993

PRODUCT NAME: Chlorhexidine Gluconate Oral Rinse

ANDA/AADA NUMBER: 73-695

FIRM NAME: Colgate-Palmolive

NAME AND TITLE OF PERSON WITH
WHOM CONVERSATION WAS HELD: Paul Okarma, Reg Affairs
Valerie Vashio, OGD

PARTICIPANT(S) TELEPHONE: 908-878-7323

MINUTES OF CONVERSATION:

Phoned re firm's 8/11/93 submission requesting meeting. Informed firm meeting request is for administrative details regarding OGD processing of ANDA. Advised that our procedure has been told to the firm in several conversations previously with the support branch. The 5/93 amendment is in Q and will be reviewed pursuant to standard FIFR policy. We cannot and will not make an exception for this ANDA unless firm shows that OGD has erred in its processing. My review of the file indicates no such error. Branch 2 review time is 5-6 months. Firm should expect review in Oct-Nov, 1993.

Okarma questioned transfer of ANDA to different branch and effect on review time. I stated this was done by drug category, not by ANDA and was designed to increase quality and consistency of reviews. Transfer involved many ANDAs and impact on any single submission could not be considered.

I stated once the amendment is reviewed and if firm receives a NA letter, we will reconsider request for meeting at that time.

Dr. Okarma did not seem pleased with this decision but did seem resigned to it.

NAME OF OGD REPRESENTATIVE: Michael J. Šmela, Jr. /S/

SIGNATURE OF OGD REPRESENTATIVE: /S/ 8/19/93

DIVISION/BRANCH: Division of Chemistry 1, Branch 2 (HFD-634)

RECORD OF TELEPHONE CONVERSATION

Dr. Okarma called to see if we had received the fascimile dated January 6, 1994 regarding the site at which the stability data for the exhibit batch were generated. I confirmed that we had received the transmission.

He apologized for the confusion and again stated that these data were not generated at Colgate's facility in New Jersey. They were generated at the firm's testing facility in Canton, Massachusetts. The Canton facility has subsequently been closed.

Dr. Okarma agreed to submit a supplemental new drug application post-approval to provide for a facility in Texas to perform the stability storage and analytical testing for the production batches.

DATE
January 7, 1994

AADA NUMBER
73-695

IND NUMBER

TELECON

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

PRODUCT NAME
Chlorhexidine Gluconate Oral Rinse, 0.12%

FIRM NAME
Colgate-Palmolive

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Paul J. Okarma, Ph.D.
Associate Director
Regulatory Affairs

TELEPHONE NUMBER

(908) 878-7323

SIGNATURE

/S/

1/7/94

NOTICE OF APPROVAL
NEW DRUG APPLICATION OR SUPPLEMENT

NDA NUMBER: 73-695

DATE APPROVAL LETTER ISSUED: AP 1.14.94

TO: Press Relations Staff (HFI-40)

FROM: ☑ Bureau of Drugs ☐ Bureau of Veterinary Medicine

ATTENTION

Forward original of this form for publication only after approval letter has been issued and the date of approval has been entered above.

TYPE OF APPLICATION: ☐ ORIGINAL NDA ☐ SUPPLEMENT TO NDA ☑ ~~ABBREVIATED~~ ORIGINAL NDA ☐ SUPPLEMENT TO ANDA

CATEGORY: ☑ HUMAN ☐ VETERINARY

TRADE NAME (or other designated name) AND ESTABLISHED OR NONPROPRIETARY NAME (if any) OF DRUG:

Chlorhexidine Gluconate

DOSAGE FORM: Oral Rinse

HOW DISPENSED: ☒ Rx ☐ OTC

ACTIVE INGREDIENT(S) (as declared on label. List by established or nonproprietary name(s) and include amount(s). If amount to be declared on label.)

Chlorhexidine Gluconate, 0.12%

NAME OF APPLICANT (Include City and State)

Colgate-Palmolive Co.
Piscataway, N.J. 08854-5596

PRINCIPAL INDICATION OR PHARMACOLOGICAL CATEGORY

Microbicidal Activity - Reduction of plaque

COMPLETE FOR VETERINARY ONLY

ANIMAL SPECIES FOR WHICH APPROVED

COMPLETE FOR SUPPLEMENT ONLY

CHANGE APPROVED TO PROVIDE FOR

FORM PREPARED BY

NAME: /S/ DATE: 11/30/93

FORM APPROVED BY

NAME: /S/ (pending labeling + EER) DATE: 12/1/93

FORM FD 644 (3/75) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

M E M O R A N D U M

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

DATE: January 14, 1994

FROM: Chief, Review Support Branch /S/ 1/14/94

SUBJECT: Approvability of ANDA 73-695 for Chlorhexidine Gluconate Oral Rinse (PerioGard) Submitted by Colgate-Palmolive Company

TO: The Record

THROUGH Acting Deputy Director, OGD /S/ 1/14/94

/S/ 1/14/94

This memorandum is written to clarify the current CGMP status of ANDA 73-695.

Throughout the review process the chemistry reviewer understood that stability testing for the exhibit batch was performed by the manufacturer of the finished dosage form, or by the applicant in Piscataway, New Jersey.

However, in a communication from Paul J. Okarma, Ph.D. dated January 6, 1994, we were informed that the stability data for the exhibit batch was performed at the firm's Canton, Massachusetts facility, but that the testing was to be transferred to the firm's facility in Dallas, Texas. An amended EER for the Canton facility was forwarded to the Office of Compliance at that time.

We were informed by David Doleski/OC that the firm's Canton, MA facility was last inspected and profiled in 1988 and was currently out of date. He also could find no record of this facility being profiled for stability testing.

I phoned Dr. Okarma and discussed the situation with him. He stated that the Canton facility was used for stability testing for many of their marketed drug products and offered to FAX a copy of the November 21, 1988 inspection report. I received the copy of the report and upon reading it determined that the inspector did address stability testing for at least two of the firms marketed products.

I returned the telephone call to Dr. Okarma and asked for a listing of other marketed products that were tested at the firm's Canton facility at the same time as Chlorhexidine Gluconate Oral Rinse was tested. He agreed to send me a FAX of this information. I also requested he to tell me if and additional stability data were available. He referred me to the firm's November 22, 1993 minor amendment (Appendix 5 page 000050 for Exhibit Batch 22617). This document does provide additional room-temperature stability data for process validation batches as well as exhibit batch 22617 requested by the chemist in a prior minor amendment not-approvable letter. The data were generated in January, February, March, April, July and November, 1993 and were reviewed by the reviewing chemist and determined to be acceptable. Upon questioning, Dr. Okarma informed me that the January through September data were obtained at the Canton, MA facility; however the November data were obtained at the firm's facility in Dallas, Texas (Colgate Oral Pharmaceuticals, 14335 Gillis Road, Dallas, Texas 75244). The November data represent 9-month data; the May through July data represent initial through 6-month controlled room-temperature data for the exhibit batch.

Subsequent to this call, I contacted Mr. Doleski who informed me that the district had inspected the Dallas facility on November 24, 1992 and found it acceptable according to the profile class for liquid testing. I completed an amended preapproval EER, took it to OC, and it was signed and returned to me by Mr. Doleski.

In the interim, I received a FAX of a communication dated January 14, 1994 from Dr. O'Karma. It contains a listing of products which were tested under the Canton, MA stability program. Those tested concurrently with chlorhexidine gluconate exhibit batch during May through September, 1993 are highlighted. The submission also states that the stability laboratory for Colgate Oral Pharmaceuticals was moved from Canton to Dallas, Texas in September 1993 and confirms that the data dated November, 1993 as submitted to the application in the firm's November 22, 1993 minor amendment were performed at the firm's Dallas, TX facility.

Discussion:

The firm has submitted additional stability data for the exhibit batch as well as the validation batches. These data were reviewed and found acceptable for approval by the chemist. However, the December data were obtained from the firm's Dallas, Texas facility. Today's communication confirms that fact.

The question of the acceptability of the data obtained at the firm's Canton, MA facility has been raised. We are unable to ascertain whether those data were collected under CGMP conditions. The facility was last inspected in 1988 and a minor FD-483 was left with the firm for resolution. We do know that the Canton facility continued until this past summer to provide stability data for chlorhexidine gluconate as well as other products the firm markets.

The firm's Dallas, Texas facility has been inspected by the district and found acceptable. A review of the stability data generated by this facility demonstrates that they are consistent with the data generated at Canton. Thus, we have a reasonable measure of assurance that the Canton data reflect the stability of the drug. The fact that the Dallas, Texas facility has been found in compliance with CGMPs and that the Canton facility was previously acceptable in 1988 also provides a similar measure of assurance.

Conclusion:

Accept the stability data generated at the firm's Canton, MA facility as being supportive of the drug's safety and effectiveness. Proceed with approval.

Addendum:

I am unsure as to why there was confusion as to the site of the stability testing. On page 22 of a submission dated October 13, 1992, the firm clearly stated that "The stability testing . . . (for the drug product) will be performed at Colgate-Hoyt/Gel Kam, One Colgate Way, Canton, MA 02021.

CC:

ANDA 73-695
Div File

MEMORANDUM TO THE RECORD