CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-832

CORRESPONDENCE

NDA No. 20-832
Correspondence

MEDI-FLEX
QUALITY THROUGH INNOVATION

February 20, 1997

Maureen Dillon-Parker
Project Manager
Division of Anti-Infective Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard HFD-520
Rockville, MD 20850

Re: Clarification of Referenced Drug Master Files
Submission of Debarment Statement

Dear Ms Parker:

The original NDA submission did not include a debarment statement. Enclosed are 8 copies of the following debarment statement to which I attest:

> Pursuant to section 306(K)(1) of the Federal Food. Drug and Cosmetic Act, the applicant certifies that, to the best of its knowledge and belief, the applicant did not and will not use in any capacity, in connection with this application, the services of any person listed pursuant to section 306(e) as debarred under subsections 306(a) or (b) of the Act.

The investigators at IMTCI have been known to me for a number of years, and the investigators at were reviewed closely to provide assurance that FDA 483 reports of the past had been specifically addressed with no debarment and that corrections in research practices had led to a specific FDA review with current good standing.

Regarding the NDA and DMF numbers for which access is granted, I have contacted Zeneca and was provided confirmation that access is granted to NDA number 17-768 which Zeneca says is an NDA covering the chlorhexidine gluconate [redacted] from which other formulations are prepared. The basic pharm/tox and chemistry data for their regulatory packages is said to be included in this NDA 17-768. The DMF numbers [redacted] were also clarified as the correct DMF.

I would note that a third DMF is listed in the NDA application form and this DMF is not related to the chlorhexidine gluconate per se. This DMF [redacted] relates to the [redacted] which is no longer used in the final formulation. This DMF is from the company [redacted] and continued reference is made in this NDA because certain of the formulations studied included this agent. [redacted]

Thank you.

Sincerely,

Patrick D. McGrath, Ph.D.
Director, Research and Development

MEDI-FLEX HOSPITAL PRODUCTS, INC. • 8717 W. 110th Street, Suite 750 • Overland Park, KS 66210-2103 • 913-451-0880 • 1-800-523-0502

Beckloff Associates, Inc.
Pharmaceutical Research and Development

OFFICE OF THE
PRESIDENT

January 13, 2000

Food and Drug Administration
Center for Drug Evaluation and Research
Attention: Central Document Room
12229 Wilkins Avenue
Rockville, Maryland 20852-1833

Re: NDA No. 20-832
Chlorhexidine Gluconate 2% (w/v) Topical Solution
Response to February 20, 1998, FDA Complete Response Letter
Amendment to NDA Section 8, Clinical, and Section 10, Statistical

Sir/Madam:

Reference is made to NDA No. 20-832 for Chlorhexidine Gluconate 2% (w/v) Topical Solution which was submitted to the FDA on January 8, 1997, and the subsequent submissions to the FDA dated August 8, October 6, and November 26, 1997. Reference is also made to the February 20, 1998, Complete Response Letter from Gary K. Chikami, M.D., Director, Division of Anti-Infective Drug Products, and Debra L. Bowen, M.D., Director, Division of Over-the-Counter Drug Products. For ease of review, a copy of the February 20, 1998, FDA Complete Response Letter is included in Attachment 1.

Submitted herewith is an Amendment to NDA No. 20-832 to address all points raised in the FDA Complete Response Letter. The information which has been requested is presented in Attachment 2. In order to aid in the review of the information provided, each of the items discussed in the letter from Drs. Chikami and Bowen is listed separately followed by comments and/or explanations. In reviewing the enclosed information, please note that the proposed indication for use of Chlorhexidine Gluconate 2% (w/v) Topical Solution is "patient preoperative skin preparation" per our NDA Amendment dated February 27, 1998. We request that the review clock for NDA No. 20-832 be restarted since this Amendment completely responds to all points raised in the FDA Complete Response Letter.

Telephone 913-451-3955 • Facsimile 913-451-3846 • beckmail@beckloff.com
Commerce Plaza II, Suite 720 • 7400 West 110th Street • Overland Park, Kansas 66210 USA
Metropolitan Kansas City • http://www.beckloff.com

This Amendment to NDA No. 20-832 consists of 12 volumes. Per a telephone discussion with Maureen Dillon-Parker, Project Manager, Division of Anti-Infective Drug Products, on December 13, 1999, this NDA Amendment is submitted in triplicate and contains one archival copy (blue binding), one clinical technical review copy (brown binding), and one statistical technical review copy (green binding).

Sincerely,

Michael C. Beckloff
President and Chief Executive Officer
Beckloff Associates, Inc.
Agent for Medi-Flex Hospital Products, Inc.

ffw

Enclosures

cc: Mr. A. Brandmeyer

12220fda7005.doc

Beckloff Associates, Inc.
Pharmaceutical Research and Development

OFFICE OF THE
PRESIDENT

February 3, 2000

Ms. Maureen Dillon-Parker
Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective Drug Products
HFD 520/S-307
9201 Corporate Boulevard
Rockville, Maryland 20850

Re: NDA No. 20-832
Chlorhexidine Gluconate 2% (w/v) Topical Solution
Response to February 20, 1998, FDA Complete Response Letter
Amendment 1 to NDA Section 8, Clinical, and Section 10, Statistical
Additional Requested Information: Index, Additional Copies, and Data Disks

Dear Ms. Dillon-Parker,

Reference is made to the Amendment to NDA No. 20-832 which was submitted to the FDA on January 13, 2000. In addition, reference is made to recent telephone discussions between you and M. Sylvestri, J. Hibbard, and K. Oliva-Whalen of Beckloff Associates, Inc., regarding this NDA Amendment.

Per your request, enclosed are the following items relative to the NDA Amendment submitted on January 13, 2000, in order to enable the FDA to commence review:

- Index: one archival copy (blue binding), one clinical technical review copy (brown binding), one statistical technical review copy (green binding), and one desk copy (black binding) (i.e., four copies total)

- Volume 1, including index: two copies (black binding) for the OTC Division and one desk copy (black binding) (i.e., three copies total)

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- Volume Table of Contents: one copy of the individual volume tables of contents in one black binder
- Data Disk and Contents: Three diskettes, each containing SAS data files for Protocol No. 990326.HTR performed by Hill Top Research (HTR Study No. 103691) and for Protocol No. 990326.MBT performed by MicroBioTest (MBT Study No. 371-104) with a hard copy of the disk contents, in individual slipsheets in one black binder

Per the discussions, it is our understanding that you will place the additional information in the FDA files as appropriate.

[redacted]

REDACTIONS MADE
BY APPLICANT

Please do not hesitate to contact me or Kathy Oliva-Whalen at 913-451-3955 should you have any questions or require additional information. Thank you for your assistance in this matter.

Sincerely,

Michael C. Beckloff
President and Chief Executive Officer
Beckloff Associates, Inc.
Agent for Medi-Flex Hospital Products, Inc.

erm

Enclosures

cc: Mr. A. Joseph Brandmeyer

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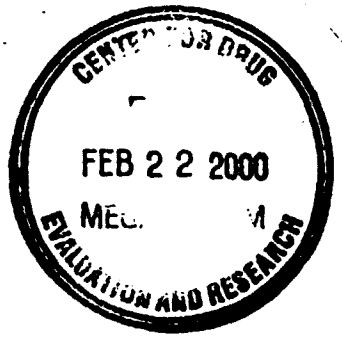
Beckloff Associates, Inc.
Pharmaceutical Research and Development

OFFICE OF THE
PRESIDENT

NDA ORIG

BL



February 21, 2000

Ms. Maureen Dillon-Parker
Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective Drug Products
HFD 520/S-307
9201 Corporate Boulevard
Rockville, Maryland 20850

Re: NDA No. 20-832
Chlorhexidine Gluconate 2% (w/v) Topical Solution
Response to February 20, 1998, FDA Complete Response Letter
Additional Requested Information: Electronic Version of Package Insert

Dear Ms. Dillon-Parker,

Reference is made to the Amendments to NDA No. 20-832 which were submitted to the FDA on January 13 and February 3, 2000. Reference is also made to our telephone discussion of February 15, 2000, regarding your request for an electronic version of the package insert for chlorhexidine gluconate 2% (w/v) topical solution.

As we discussed, the color mock-up labeling included in the NDA Amendment was prepared using Quark on a Macintosh computer. However, per our discussion, we have included in this submission a diskette containing an electronic version of the package insert text in Word for Windows. We have also included a hard copy of the text for your reference.

We are hopeful that you will find the electronic version of the package insert text useful during the review process. Please do not hesitate to contact me or Kathy Oliva-Whalen at

ORIGINAL

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Metropolitan Kansas City • http://www.beckloff.com

913-451-3955 should you have any questions or require additional information.

Sincerely,

Michael C. Beckloff
President and Chief Executive Officer
Beckloff Associates, Inc.
Agent for Medi-Flex Hospital Products, Inc.

erm

Enclosures

cc: Mr. A. Joseph Brandmeyer
Dr. J. Hibbard

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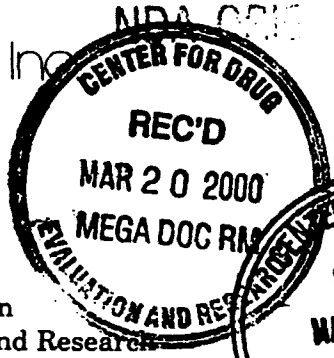
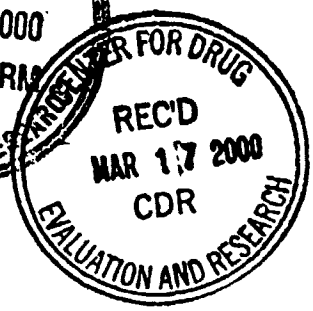
APPEARS THIS WAY
ON ORIGINAL

Beckloff Associates, Inc.
Pharmaceutical Research and Development
Founded 1976

NDA 20-832





March 16, 2000

Food and Drug Administration
Center for Drug Evaluation and Research
Attention: Central Document Room
12229 Wilkins Avenue
Rockville, Maryland 20852-1833

Re: NDA No. 20-832
Chlorhexidine Gluconate 2% (w/v) Topical Solution
Amendment 2, NDA Section 4, Chemistry

Sir/Madam:

BC

Reference is made to NDA No. 20-832 for Chlorhexidine Gluconate 2% w/v Topical Solution which was submitted to the FDA on January 8, 1997, and the subsequent submissions to the FDA dated August 8, October 6, and November 26, 1997, and January 13, 2000. Reference is also made to telephone discussions between M. Dillon-Parker, Project Manager, Division of Anti-Infective Drug Products, and K. Oliva-Whalen, Beckloff Associates, Inc., on March 14, 2000.

Submitted herewith is an Amendment to Section 4, Chemistry, of NDA No. 20-832. This information is complementary to the CMC information contained in the original NDA and pertains to drug product in the new 3.0-mL applicator.

The information in this Amendment is organized as follows:

- Table of Contents
- Attachment 1 provides information regarding the supplier of the drug substance, chlorhexidine gluconate 20%, including a letter of Authorization to Reference their DMF, release specifications, and a Certificate of Analysis.
- Attachment 2 contains a revised description of the manufacturing process. The revised manufacturing information also includes modification of the applicator identified in the above-referenced NDA (i.e., packaging of 3.0-mL ampoules into applicators).
- Attachment 3 provides the current Master Production and Control Record (MPR), including the sterilization procedure.
- Attachment 4 includes release specifications and test methods for the drug product.

DUPLICATE

Telephone 913-451-3955 • Facsimile 913-451-3846 • beckmail@beckloff.com
Commerce Plaza II, Suite 720 • 7400 West 110th Street • Overland Park, Kansas 66210 USA
Metropolitan Kansas City • http://www.beckloff.com

- Attachment 5 includes updated stability data for the [redacted] applicators and new stability data for the 3.0-mL applicator.
- Attachment 6 provides draft labeling.
- Attachment 7 provides a copy of the Environmental Impact Assessment for the manufacture of Chlorhexidine Gluconate 2% (w/v) Topical Solution submitted to the FDA on October 6, 1997, which is still applicable.

This Amendment to NDA No. 20-832 consists of one volume. This NDA Amendment is submitted in triplicate and contains one archival copy (blue binding) and two chemistry technical review copies (red binding).

Please do not hesitate to contact me or Michael Beckloff at 913-451-3955 should you have any questions regarding this submission or require additional information.

Sincerely,

Kathy Oliva-Whalen

Kathy Oliva-Whalen
Vice President, Pharmaceutical Development
Beckloff Associates, Inc.
Agent for Medi-Flex Hospital Products, Inc.

vcg

Enclosures

cc: Mr. A. Joseph Brandmeyer, Medi-Flex Hospital Products, Inc.
Mr. O. Cordova, Medi-Flex Hospital Products, Inc.
Ms. Maureen Dillon-Parker, Food and Drug Administration
(cover letter only)

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Beckloff Associates, Inc.
Pharmaceutical Research and Development
Founded 1976

April 6, 2000

Ms. Maureen Dillon-Parker
Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective Drug Products
HFD 520/S-307
9201 Corporate Boulevard
Rockville, Maryland 20850

Re: NDA No. 20-832
Chlorhexidine Gluconate 2% (w/v) Topical Solution
Additional Requested Information: Mock-Up of Final Product Packaging

Dear Ms. Dillon-Parker:

Reference is made to the Amendments to NDA No. 20-832 which were submitted to the FDA on January 13 and February 3, 2000. Reference is also made to our telephone discussion of March 14, 2000, regarding your request for a sample of chlorhexidine gluconate 2% (w/v) topical solution in the proposed packaging.

Per your request, enclosed is a mock-up of the final product in the proposed packaging, labeled and packaged in accordance with the information included in Volume 1, Appendices 1–5, of the Amendment to NDA 20-832 submitted on January 13, 2000. The mock-up of the final product packaging consists of one carton (intermediate packaging) containing 24 applicators, each of which is packaged in a separate pouch (immediate container). As described in Volume 1, Appendix 5, of the January 13 NDA Amendment, one copy of the package insert has been placed on top of the pouches in the carton.

Please be advised that the mock-up pouches and carton are stamped "non-sterile prototype." In addition, although the mock-up consists of 24 pouches in one carton, the final marketed package will contain 25 pouches per intermediate carton as indicated in the January 13 NDA Amendment.

With respect to the labeling included on the enclosed sample packaging, please note the following:

- For the sample packaging, only 5 pouches (immediate container) have been labeled as an example.
- The top and right side panel labels on the intermediate package (carton) were not included in Appendices 1–4 of the January 13 NDA Amendment.

We are hopeful that you will find the enclosed sample product packaging useful during the review process. Please do not hesitate to contact Michael Beckloff at 913-451-3955 should you have any questions or require additional information.

Sincerely,

Kathy Oliva-Whalen
Vice President, Pharmaceutical Development
Beckloff Associates, Inc.
Agent for Medi-Flex Hospital Products, Inc.

vcg

Enclosure

Cc: Mr. A. Brandmeyer
Mr. O. Cordova
Dr. J. Hibbard

MEDI-FLEX®

May 10, 2000

Ms. Maureen Dillon-Parker
Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective Drug Products
HFD 520/S307
9201 Corporate Boulevard
Rockville, Maryland 20850

Re: NDA No. 20-832
Chlorhexidine Gluconate 2% (w/v) Topical Solution
Improved 3-mL Applicator with New Resin

Dear Ms. Dillon-Parker,

Reference is made to the April 6, 2000, submission containing mock-ups of the final product packaging for chlorhexidine gluconate 2% (w/v) topical solution. Reference is also made to your telephone discussion with Michael Beckloff, Beckloff Associates, Inc., on May 9, 2000, regarding breakage of the 3-mL applicators included in this submission.

Please be advised that the applicators contained in the April 6 submission were prototypes. Medi-Flex Hospital Products, Inc., has identified an issue with the compatibility of the [redacted] in the applicator and the alcohol in the drug product solution and has improved the 3-mL applicator. [redacted] Fifteen (15) samples of the improved 3-mL applicators with new resin are enclosed for your evaluation.

Should you have any further questions, please do not hesitate to contact Michael Beckloff at (913) 451-3955.

Sincerely,

Orlando Cordova
Vice President of Quality Assurance & Regulatory Affairs

Enclosure

Cc: Mr. A. Brandmeyer, Medi-Flex Hospital Products, Inc.
Mr. Michael Beckloff, Beckloff Associates, Inc.

Beckloff Associates, Inc.
Pharmaceutical Research and Development

OFFICE OF THE
PRESIDENT

May 11, 2000

Food and Drug Administration
Center for Drug Evaluation and Research
Attention: Central Document Room
12229 Wilkins Avenue
Rockville, Maryland 20852-1833

Re: NDA No. 20-832
Chlorhexidine Gluconate 2% (w/v) Topical Solution
Amendment 3, NDA Section 8, Clinical; and Section 10, Statistical

Sir/Madam:

Reference is made to NDA No. 20-832 for Chlorhexidine Gluconate 2% (w/v) Topical Solution which was submitted to the FDA on January 8, 1997, and the subsequent submissions to the FDA dated August 8, October 6, and November 26, 1997, and January 13 and March 16, 2000.

Submitted herewith is an Amendment to Section 8, Clinical and Section 10, Statistical, of NDA No. 20-832. This Amendment consists of a corrected page for the Clinical Statistical Report for Protocol No. 990326.HTR which was submitted to the Agency as an Amendment to NDA No. 20-832 on January 13, 2000. The affected page was located in Volume 2, page 0006 of the January Amendment.

Revisions were made as follows:

- The second sentence of the second paragraph that reads, *One hundred twenty eight (128) of these subjects had "qualifying screening counts" and were treated with the test products* has been changed to read, *One hundred thirteen (113) of these subjects had qualifying screening counts and one hundred six (106) were treated with the test products.*

- The first sentence of the third paragraph which reads, *One hundred six (106) of these subjects, who had baseline counts (on the day treatment was applied) met the "study criteria for inclusion," completed the study* has been changed to read, *Eighty five (85) subjects, who had baseline counts (on the day treatment was applied) that met the "study criteria for inclusion," completed the study.*
- A line was added to the summary of demographic information to indicate that no demographics were available on seven subjects.

A copy of the revised page is included in this submission.

This NDA Amendment is submitted in triplicate and contains one archival copy (blue binding), one clinical technical review copy (brown binding), and one statistical technical review copy (green binding).

Sincerely,

Michael C. Beckloff

Michael C. Beckloff
President and Chief Executive Officer
Beckloff Associates, Inc.
Agent for Medi-Flex Hospital Products, Inc.

Enclosure

sel

cc: Mr. A. J. Brandmeyer, Medi-Flex Hospital Products, Inc.
Ms. R. Minion, Medi-Flex Hospital Products, Inc.
Mr. O. Cordova, Medi-Flex Hospital Products, Inc.
Ms. M. Dillon-Parker, Food and Drug Administration (cover letter only)

Beckloff Associates, Inc.
Pharmaceutical Research and Development

OFFICE OF THE
PRESIDENT

May 17, 2000

Ms. Maureen Dillon-Parker
Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective Drug Products
HFD 520/S307
9201 Corporate Boulevard
Rockville, Maryland 20850

Re: NDA No. 20-832
Chlorhexidine Gluconate 2% (w/v) Topical Solution
Improved Applicators Containing Chlorhexidine Gluconate 2%
with 70% Isopropyl Alcohol

Ms. Dillon-Parker:

Reference is made to the May 10, 2000, submission containing samples of the improved 3-mL applicator with the new resin for chlorhexidine gluconate 2% (w/v) topical solution. Reference is also made to our telephone discussion of May 17, 2000. As we discussed, due to time restrictions, sample availability, and considering that our focus was on the improved [redacted] the samples provided were filled with aqueous chlorhexidine gluconate solution. As you are aware, Chloraprep™ drug product is comprised of chlorhexidine gluconate 2% with 70% isopropyl alcohol. The aqueous chlorhexidine gluconate solution does not flow as well as the chlorhexidine gluconate 2% with 70% isopropyl alcohol. This accounts for the reason a potential flow issue was noted. We are including ten samples of the improved 3-mL applicator with the new resin containing chlorhexidine gluconate 2% with 70% isopropyl alcohol for your evaluation.

Please do not hesitate to contact me should you have further questions regarding this matter.

Sincerely,

Michael C. Beckloff

Michael C. Beckloff
President and Chief Executive Officer

ffw

Enclosures

cc: Mr. A. Brandmeyer, Medi-Flex Hospital Products, Inc.
Mr. O. Cordova, Medi-Flex Hospital Products, Inc.
Ms. R. Minion, Medi-Flex Hospital Products, Inc.

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Telephone 913 451 2055 • F

Beckloff Associates, Inc.
Pharmaceutical Research and Development

OFFICE OF THE
PRESIDENT

May 25, 2000

Food and Drug Administration
Center for Drug Evaluation and Research
Attention: Central Document Room
12229 Wilkins Avenue
Rockville, Maryland 20852-1833

Re: NDA No. 20-832
Chlorhexidine Gluconate 2% (w/v) Topical Solution
Amendment 4, NDA Section 4, Chemistry

Sir/Madam:

Reference is made to NDA No. 20-832 for Chlorhexidine Gluconate 2% (w/v) Topical Solution which was submitted to the FDA on January 8, 1997, and the subsequent submissions to the FDA dated August 8, October 6, and November 26, 1997, and January 13, March 16, and May 11, 2000.

Submitted herewith is a Minor Amendment to Section 4, Chemistry, of NDA No. 20-832. This Amendment consists of an Authorization to Reference Letter for Drug Master File

A copy of this letter was provided via telefax to Ms. Maureen Dillon-Parker on May 25, 2000, per our telephone discussion.

This NDA Amendment is submitted in duplicate and contains one archival copy (blue binding) and one chemistry review copy (red binding).

Sincerely,

Michael C. Beckloff
President and Chief Executive Officer
Beckloff Associates, Inc.
Agent for Medi-Flex Hospital Products, Inc.

Enclosure

cc: Mr. A. J. Brandmeyer, Medi-Flex Hospital Products, Inc.
Ms. R. Minion, Medi-Flex Hospital Products, Inc.
Mr. O. Cordova, Medi-Flex Hospital Products, Inc.
Ms. M. Dillon-Parker, Food and Drug Administration (cover letter only)

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Metropolitan Kansas City • http://www.beckloff.com

Beckloff Associates, Inc.
Pharmaceutical Research and Development

OFFICE OF THE
PRESIDENT

July 6, 2000

Food and Drug Administration
Drug Master File Staff
Center for Drug Evaluation and Research
Attention: Central Document Room
12229 Wilkins Avenue
Rockville, Maryland 20852-1833

Re: NDA No. 20-832
Chlorhexidine Gluconate 2% (w/v) Topical Solution
Amendment 6, NDA Section 7, Clinical Microbiology

Sir/Madam:

Reference is made to NDA No. 20-832 for Chlorhexidine Gluconate 2% (w/v) Topical Solution which was submitted to the FDA on January 8, 1997.

Submitted herewith is an Amendment to Section 7, Clinical Microbiology, of NDA No. 20-832, containing a detailed protocol of the MicroBioTest neutralizer validation study as requested in the telefax dated June 28, 2000, from Maureen Dillon-Parker, Project Manager, Anti-Infectives.

This NDA Amendment is submitted in duplicate and contains one archival copy (blue binding) and one microbiology review copy (white binding).

Sincerely,

Michael C. Beckloff
President and Chief Executive Officer
Beckloff Associates, Inc.
Agent for Medi-Flex Hospital Products, Inc.

Enclosure

cc: Mr. A.J. Brandmeyer, Medi-Flex Hospital Products, Inc.
Ms. R. Minion, Medi-Flex Hospital Products, Inc.
Mr. O. Cordova, Medi-Flex Hospital Products, Inc.
Ms. M. Dillon-Parker, Food and Drug Administration

Telephone 913-451-3955 • Facsimile 913-451-3846 • beckmail@beckloff.com
Commerce Plaza II, Suite 720 • 7400 West 110th Street • Overland Park, Kansas 66210 USA
Metropolitan Kansas City • http://www.beckloff.com

Beckloff Associates, Inc.
Pharmaceutical Research and Development

OFFICE OF THE PRESIDENT

July 7, 2000

Ms. Maureen Dillon-Parker
Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective Drug Products
HFD 520/S307
9201 Corporate Boulevard
Rockville, Maryland 20850

Re: NDA No. 20-832
Chlorhexidine Gluconate 2% (w/v) Topical Solution
Additional Requested Information: Revised Product Labeling

Ms. Dillon-Parker:

We are proposing the following revisions to the draft labeling you provided in your telefaxes of June 28 and July 3, 2000. A description of the revisions are indicated below and correspond to the numbers in the left-hand margins of the attached Principal Display Panel-Dispenser Box and Drug Facts labeling. Please note that this is still in a draft format. The specifications as defined in 21 CFR 201.66 will be addressed as soon as we have finalized the text.

Principal Display Panel-Dispenser Box Labeling (Attachment 1)

1. The trademark symbol has been included following the name ChloraPrep™.

2. The terminology one-step has been added.

   Please note that the term "one-step" refers to the fact that ChloraPrep™ is used as a one-step (single) application to the skin. It does not refer to the pressing of the sponge against the skin. Because two-step antiseptic applications are commonly performed in surgical settings, we believe the term "one-step" is appropriate to indicate that only a single application of ChloraPrep™ is needed.

Telephone 913-451-3955 • Facsimile 913-451-3846 • beckmail@beckloff.com
Commerce Plaza II, Suite 720 • 7400 West 110th Street • Overland Park, Kansas 66210 USA
Metropolitan Kansas City • http://www.beckloff.com

3. The heading "Active Ingredients:" has been added. Chlorhexidine Gluconate 2% (w/v) and Isopropyl Alcohol have been listed independently.

[redacted]

5. The statement under "Use:" has been revised to more clearly define the indication for ChloraPrep™.

6. Under the heading "Warnings," each warning statement has been bulleted.

7. Under the heading "Do not use," the statement regarding use in children less than two months of age has been revised. Medi-Flex does not have information and/or data addressing excessive irritation or increased drug absorption for children under two months of age.

8. Under the heading "Do not use," the statement regarding allergic reactions has been revised to more clearly define that ChloraPrep™ should not be used on patients with known allergies to chlorhexidine gluconate or isopropyl alcohol.

9. Under the heading "When using this product," the single-use statement has been deleted. Our studies indicate that potential skin irritation does not result from multiple applications of ChloraPrep™.

10. Under the heading "When using this product," the statement regarding eyes, ears, and mouth has been revised to indicate that serious or permanent injury may result if the product comes into contact with these areas. The last sentence of this section beginning with "if contact occurs..." has been combined with the statement regarding eyes, ears, and mouth because this is an instruction as to the action required if the ChloraPrep™ comes into contact with these areas. Additionally, we have added "and contact a physician" as an added action.

[redacted]

[redacted]

[redacted]

Drug Facts Labeling (Attachment 2)

1. The statement under "Use" has been revised to more clearly define the indication for ChloraPrep™.

2. Under the heading "Warnings," each warning statement has been bulleted.

3. Under the heading "Do not use," the statement regarding use in children less than two months of age has been revised. Medi-Flex does not have information and/or data addressing excessive irritation or increased drug absorption for children under two months of age.

4. Under the heading "Do not use," the statement regarding allergic reactions has been revised to more clearly define that ChloraPrep™ should not be used on patients with known allergies to chlorhexidine gluconate or isopropyl alcohol.

5. Under the heading "When using this product," the single-use statement has been deleted. Our studies indicate that potential skin irritation does not result from multiple applications of ChloraPrep™.

6. Under the heading "When using this product," the statement regarding eyes, ears, and mouth has been revised to indicate that serious or permanent injury may result if the product comes into contact with these areas. The last sentence of this section beginning with "if contact occurs..." has been combined with the statement regarding eyes, ears, and mouth because this is an instruction as to the action required if the ChloraPrep™ comes into contact with these areas. Additionally, we have added "and contact a physician" as an added action.

[redacted]

8. Under the heading "Other information," the storage temperature has been revised to be consistent with the storage condition indicated on the Principal Display Panel-Dispenser Box label.

9. Under the heading "Inactive ingredients," USP Purified Water has been indicated. No other inactive ingredients are included in ChloraPrep™.

10. Under the heading "Questions?" the 1-800-523-0502 telephone number, manufacturer, and location have been added.

Per your request, this document is being submitted in triplicate.

If you have any questions or require additional information, please do not hesitate to contact us.

Best regards,

Michael C. Beckloff
President and Chief Executive Officer
Beckloff Associates, Inc.
Agent for Medi-Flex Hospital Products, Inc.

cc: Mr. A.J. Brandmeyer, Medi-Flex Hospital Products, Inc.
Ms. R. Minion, Medi-Flex Hospital Products, Inc.
Mr. O. Cordova, Medi-Flex Hospital Products, Inc.

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MEMORANDUM

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

DATE: July 10, 2000

TO: Michael Beckloff
President and Chief Executive Officer
Beckloff Associates, Inc. for Medi-Flex Hospital Products, Inc.
#913-451-3846

FROM: Maureen Dillon-Parker
Project Manager, Anti-Infectives Division
Food and Drug Administration

THROUGH: Gary Chikami, Division Director, Anti-Infectives
Alexander Rakowsky, Team Leader, Clinical, Anti-Infectives

SUBJECT: NDA 20-832 ChloraPrep™ (Chlorhexidine Gluconate 2% (w/v) Topical Solution)

We have reviewed your facsimile of July 7, 2000, containing revised product packaging for NDA 20-832 in response to the facsimiles of June 28, and July 3, 2000, and have the following comments:

PRINCIPAL DISPLAY PANEL – DISPENSER BOX LABELING

1. The proposed change is acceptable.

2. Your comments regarding the use of the term "One-Step" were conveyed to the Office of Post-Marketing Drug Risk Assessment. This Office is currently reviewing the submission and further comments will be conveyed upon completion of their review.

3. The proposed change is acceptable.

4. The proposed change is acceptable.

5. The indication should be revised to read as originally proposed by the Division. This statement is in conformance with the "Tentative Final Monograph" requirements and is mandated for all products of this type by the year 2002.

6. The proposed change is acceptable.

7. The Division has consulted with our experts in the Division of Dermatological and Dental Drug Products. As a result of that consultation and the results of the irritation studies submitted with the original NDA, it is felt that there is insufficient information to assure the safety of this product when used in children less than 2 months of age. You are invited to propose studies which establish the safety of this product in that age group. Until such studies are completed, the labeling should be revised as recommended.

8. The proposed change is acceptable.

9. The proposed change is acceptable.

10. The proposed change is acceptable.

11. The proposed change is acceptable.

12. The proposed change is acceptable.

13. The proposed change is acceptable. Additionally, it is recommended that the word "each" also be spelled out. Please also note comment #8 under the DRUG FACTS labeling.

DRUG FACTS LABELING

General Comment:

The Warning Statement as proposed in the facsimile of June 28th, 2000, should be placed in the labeling following the heading, prior to the start of Drug Facts. The statement should read:

> **WARNING. FLAMMABLE. KEEP AWAY FROM FIRE OR FLAME. DO NOT USE WITH ELECTROCAUTERY PROCEDURES.**

1. See #5 above, same comment applies.

2. The proposed change is acceptable.

3. See #7 above, the same comment applies.

4. The proposed change is acceptable.

5. The proposed change is acceptable.

6. The proposed change is acceptable.

7. The word "once" should be removed because there are no instructions to the user on what to do if the product does not flow after one pinch of the wings. Additionally, the first word following each bullet in this section should start with a lower case letter.

8. The storage conditions for both the DRUG FACTS and the PRINCIPAL DISPLAY PANEL Box should read "20°-25°C (68°-77°F)". We apologize for the discrepancy between the facsimiles.

9. The addition of Purified Water is acceptable, however, the "P" and the "W" must be in lower case.

10. The addition of the information in this section is acceptable. Additionally, if information on the times of operation (e.g., 9a.m. – 5p.m. EST) are available, this should also be stated.

Beckloff Associates, Inc.
Pharmaceutical Research and Development

OFFICE OF THE PRESIDENT

July 11, 2000

Ms. Maureen Dillon-Parker
Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective Drug Products
HFD 520/S307
9201 Corporate Boulevard
Rockville, Maryland 20850

Re: NDA No. 20-832
Chlorhexidine Gluconate 2% (w/v) Topical Solution
Additional Requested Information: Revised Product Labeling

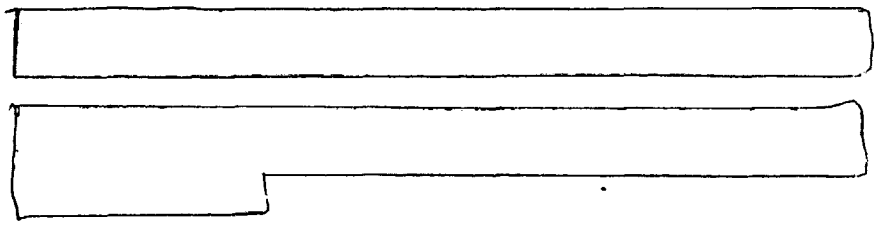
Ms. Dillon-Parker:

We have revised the draft labeling based on your telefax of July 10, 2000, and our telephone discussion of today. A description of the revisions are indicated below and correspond to the numbers in the left-hand margins of the attached Principal Display Panel-Dispenser Box and Drug Facts labeling. Please note text for side panels have been added. The specifications as defined in 21 CFR 201.66 will be addressed as soon as we have finalized the text.

Principal Display Panel-Dispenser Box Labeling (Attachment 1)

1. Per our discussions, the Principle Display Panel has been revised.

2. The registered trademark "®" has been added.



Telephone 913-451-3855 • Facsimile 913-451-3846 • beckmail@beckloff.com
Commerce Plaza II, Suite 720 • 7400 West 110th Street • Overland Park, Kansas 66210 USA
Metropolitan Kansas City • http://www.beckloff.com

5. The storage conditions have been revised to read "20–25 °C (68–77 °F)." Also, the statement "Avoid freezing and excessive heat above 40 °C (104 °F)" has been added to be consistent with the Drug Facts label.

Drug Facts Labeling (Attachment 2)

1. The registered trademark "®" has been added.
2. In the header, Isopropanol has been revised to Isopropyl Alcohol for consistency.
3. The Warning Statement has been placed above the Drug Facts box as indicated by the FDA.
4. The statement under "Use" has been revised to read as originally proposed by the FDA.
5. Under the heading "Do not use," the statement regarding use in children less than two months of age has been revised to read as originally proposed by the FDA.
6. Under the heading "Directions," the first word following each bullet begins with a lower case letter.
7. Under the heading "Directions," the word "once" has been removed from the first instruction.
8. Under the heading "Other information," the storage temperature has been revised to be consistent with the storage condition indicated on the Principal Display Panel-Dispenser Box label. Also, the word "above" has been moved.
9. Under the heading "Inactive ingredients," the words "purified water" begin with lower case letters.
10. Under the heading "Questions?" the 1-800-523-0502 telephone number is bold. Also, the hours of operation have been added.

Side-Panel Labels (Attachment 3)

Based on the revisions to the Principle Display Panel-Dispenser Box Labeling, side panel labels have been added.

Per your request, this document is being submitted in triplicate.

If you have any questions or require additional information, please do not hesitate to contact us.

Best regards,

Michael C. Beckloff
President and Chief Executive Officer
Beckloff Associates, Inc.
Agent for Medi-Flex Hospital Products, Inc.

cc: Mr. A.J. Brandmeyer, Medi-Flex Hospital Products, Inc.
Ms. R. Minion, Medi-Flex Hospital Products, Inc.
Mr. O. Cordova, Medi-Flex Hospital Products, Inc.

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MEMORANDUM **OFFICE OF POST-MARKETING DRUG RISK ASSESSMENT**
CENTER FOR DRUG EVALUATION AND RESEARCH
HFD-400; Rm 15B-03

CONSULT#: 00-0111

DATE: July 11, 2000

FROM: Lauren Lee, Pharm.D., Safety Evaluator
Medication Error Prevention, HFD-400

THROUGH: Jerry Phillips, R.Ph., Associate Director
Medication Errors Prevention, HFD-400 /S/

TO: Gary Chikami, M.D., Director
Division of Anti-Infective Drug Products, HFD-520

SUBJECT: NDA No. 20-832; ChloraPrep One-Step
(chlorhexidine gluconate 2% (w/v) and isopropyl alcohol 70% (v/v))

I. INTRODUCTION:

This memorandum is in response to the letter dated July 7, 2000, in which Bechloff Associates, Inc. presented reasons for having the term, "One-Step" as part of the proprietary name. According to the firm, *"the term, "One-Step," refers to the fact that ChloraPrep is used as a one-step (single) application to the skin. It does not refer to the pressing of the sponge against the skin. Because two-step antiseptic applications are commonly performed in surgical settings, the term, "One-Step" is appropriate to indicate that only a single application of ChloraPrep is needed."*

II. BACKROUND:

The proposed proprietary name, ChloraPrep One-Step, was previously reviewed by the Office of Post-Marketing and Drug Risk Assessment (OPDRA) on June 2, 2000. We had no objections to the use of the proprietary name, ChloraPrep. However, in reference to the term, One-Step, the directions for use of the applicator state that the user must pinch the wings on the barrel to break the ampule and release the antiseptic. Then the user has to wet the applicator sponge by repeatedly pressing and releasing the sponge against the skin of the treatment area until the liquid is visible on the skin. These steps indicate that more than one step is needed to apply the drug, and therefore, having the term, One-Step, as part of the proprietary name is misleading.

III. DISCUSSION:

According to the firm, the term, "One-Step" refers to the fact that only a single application of ChloraPrep is needed, and that subsequent application is not necessary.

However, it is not obvious that the term, "One-Step", is referring to the number of applications. On the contrary, the term could imply that only one step is required in the actual act of applying the drug to the skin. In other words, the drug is applied directly to the skin when it is taken from the package. However, in this case, the user has to first pinch the wings on the barrel to break the ampule and release the antiseptic. Then the applicator sponge has to be wetted by repeatedly pressing and releasing the sponge against the skin until the liquid (drug) is visible on the skin. These steps require that more than one step is needed to apply the drug, and therefore, having the term, One-Step, as part of the proprietary name is misleading.

IV. CONCLUSION

OPDRA has no objections to the use of the proprietary name, ChloraPrep. However, we do not recommend the use of the term, One-Step, as part of the proprietary name.

/S/ 7/11/00
Lauren Lee, Pharm.D.

Concur:

/S/ 7/12/00
Jerry Phillips, RPh