CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-832

ADMINISTRATIVE DOCUMENTS

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: 3/27/2000	DUE DATE: 5/30/2000	OPDRA CONSULT #: 00-0111

TO:

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

THROUGH:

Maureen Dillon-Parker
Project Manager
(HFD-520)

PRODUCT NAME: ChloraPrep One Step (chlorhexidine gluconate 2% (w/v) and isopropyl alcohol 70% (v/v)) **NDA #:** 20-832	**MANUFACTURER:** Mediflex Hospital Products, Inc.

SAFETY EVALUATOR: Lauren Lee, Pharm.D.

OPDRA RECOMMENDATION:
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. See the checked box below.

☐ FOR NDA/ANDA WITH ACTION DATE BEYOND 90 DAYS OF THIS REVIEW
This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from the signature date of this document. A re-review request of the name should be submitted via e-mail to "OPDRAREQUEST" with the NDA number, the proprietary name, and the goal date. OPDRA will respond back via e-mail with the final recommendation.

☑ FOR NDA/ANDA WITH ACTION DATE WITHIN 90 DAYS OF THIS REVIEW
OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from this date forward.

☐ FOR PRIORITY 6 MONTH REVIEWS
OPDRA will monitor this name until approximately 30 days before the approval of the NDA. The reviewing division need not submit a second consult for name review. OPDRA will notify the reviewing division of any changes in our recommendation of the name based upon the approvals of other proprietary names/NDA's from this date forward.

/S/ 6/2/2000
Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

/S/ - 6/5/00
Peter Honig, MD
Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B-03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE RECEIVED: March 27, 2000

NDA#: 20-832

NAME OF DRUG: ChloraPrep One-Step (chlorhexidine gluconate 2% (w/v) and isopropyl alcohol 70% (v/v))

NDA HOLDER: Mediflex Hospital Products, Inc.

I. INTRODUCTION:

This consult is in response to a March 27, 2000 request by the Division of Anti-Infective Drug Products, to review the proposed proprietary drug name, ChloraPrep One-Step, regarding potential name confusion with other proprietary/generic drug names. The container label and carton labeling were reviewed for possible interventions in minimizing medication errors.

PRODUCT INFORMATION
ChloraPrep One-Step is an antiseptic proposed for patient preoperative skin preparation. It contains chlorhexidine gluconate 2% (w/v) and isopropyl alcohol 70% (v/v) for external use . This product is to be applied using a 3 mL single-use applicator. ChloraPrep One-Step is intended for professional use only without a prescription.

II. RISK ASSESSMENT

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[1,2,3] as well as several FDA databases[4] for existing drug names which sound-alike or look-alike ChloraPrep One-Step to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[5]. An expert panel discussion was conducted to review all findings from the searches.

A. EXPERT PANEL DISCUSSION

[The expert panel consists of members of OPDRA's medication error Safety-Evaluator Staff and

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[1] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Emergindex, Reprodisk, Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).
[2] American Drug Index, online version, Facts and Comparisons, St. Louis, MO.
[3] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[4] Drug Product Reference File [DPR], the Established Evaluation System [EES], the AMF Decision Support System [DSS], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, and the electronic online version of the FDA Orange Book.
[5] WWW location http://www.uspto.gov/tmdb/index.html.

a representative from the Division of Drug Marketing, Advertising and Communications (DDMAC)].

1. The panel identified Chloragel, Chloraseptic, Chloroptic, and Chlorafed, but concluded that these names do not have the potential for name confusion with ChloraPrep One-Step. Therefore, the proposed proprietary name does not pose a safety risk due to name confusion.

2. DDMAC – no comments.

B. SAFETY EVALUATOR RISK ASSESSMENT

The name, ChloraPrep, does not have the potential for name confusion with existing products since it lacks significant look-alike and sound-alike similarity with other drug names, thereby posing no significant safety risk. 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. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container label and carton labeling of ChloraPrep One-Step, OPDRA has attempted to focus on safety issues relating to possible medication errors. OPDRA has reviewed the current container label and carton labeling and has identified several areas of possible improvement, which might minimize potential user error.

A. **CONTAINER LABEL** (p 113)

1. The label reads, "3.0 mL Applicator." Since the use of terminal zeros may lead to medication errors, we recommend deleting terminal zeros in all labels and labeling. In addition, we recommend relocating this phrase so that the statement of identity (the established name followed by the pharmacological category) is located immediately beneath the proprietary name.

2. We recommend including the statement [redacted]

3. We recommend that the inactive ingredients be listed on the label to be in accordance with 21 CFR 201.100 (b) (5).

B. **CARTON LABELING** (p 111 - 112)

1. We recommend that the established names be printed in letters that are at least half as large as the letters comprising the proprietary name to be in accordance with 21 CFR 201.10 (g) (2).

2. See comments under CONTAINER LABEL.

IV. RECOMMENDATIONS:

A. 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.

B. OPDRA recommends the above labeling revisions that might lead to safer use of the product.

OPDRA would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Lauren Lee, Pharm.D. at 301-827-3243.

/S/

Lauren Lee, Pharm.D.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

/S/ 6/2/00

Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY for NDA # 20-832 SUPPL # —

Trade Name Chloraprep® **Generic Name** 2% Chlorhexidine gluconate (CHG)/ 70% isopropyl alcohol (IP
Applicant Name Medi-Flex Hospital Products **HFD-** 520

Approval Date July 14, 2000

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?
   YES /X/ NO /__/

   b) Is it an effectiveness supplement?

   YES /__/ NO /X/

   If yes, what type? (SE1, SE2, etc.) ____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /X/ NO /__/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

Form OGD-011347 Revised 8/7/95; edited 8/8/95
cc: Original NDA Division File HFD-85 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /__/ NO /X/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /__/ NO /X/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /__/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /X/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /X/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 19-422 Exidine 2%

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /X/ NO /__/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /X/ NO /__/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /__/ NO /X/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /__/ NO /__/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /__/ NO /X/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # 990326.HTR

Investigation #2, Study # 990326.MBT

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /X/
Investigation #2	YES /___/	NO /X/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES /___/	NO /X/
Investigation #2	YES /___/	NO /X/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1, Study # 990326.HTR

Investigation #2, Study # 990326.MBT

Investigation #_, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # [redacted] YES /X/ NO /__/ Explain: _____

Investigation #2

IND # ____ YES /__/ NO /__/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /__/ Explain _____ NO /X/ Explain _____

Investigation #2 !

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /X/

If yes, explain: _____

_____

_____

_____

/S/ 7-10-00

Signature Date

Title: Reg Manager

/S/ 7/14/2000

Signature of Division Director Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20832	**Trade Name:**	CHLORAPREP(CHLOROHEXIDINE GLUCONATE)2% W
Supplement Number:		**Generic Name:**	CHLORHEXIDINE GLUCONATE
Supplement Type:		**Dosage Form:**	SOL
Regulatory Action:	AP	**Proposed Indication:**	Patient preoperative skin preparation

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, Pediatric content not necessary because of pediatric waiver

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)
____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Adequate for SOME pediatric age groups
Formulation Status	
Studies Needed	
Study Status	

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

The pediatric study requirement has been fulfilled for children 2 months of age and older. The pediatric study requirement has been waived for children under 2 months of age because of safety concerns with the use of the product in this age group. 7-14-00

Pediatric labeling will be extracted from adult labeling down to the age of 2 months. It is a patient pre-op preparation and no difference in the activity of adult vs pediatric skin (>2months) should be expected.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, MAUREEN DILLON-PARKER

/S/ 7/14/00

Signature Date

Debarrment Certification

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.

2-20-97

LAW OFFICES
HOVEY, WILLIAMS, TIMMONS & COLLINS

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ESTABLISHED 1929

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November 21, 1996

Patrick D. McGrath, Ph.D.
Medi-Flex Hospital Products, Inc.
8717 W. 110th Street, Suite 750
Overland Park, KS 66210

RE: U.S. Patent Application; UNIT DOSE CHLORHEXADINE GLUCONATE (CHG) APPLICATOR HAVING EXTENDED CHG SHELF LIFE; Docket No. 24799

Dear Pat:

The above application was filed in the U.S. Patent and Trademark Office on September 30, 1996 and assigned Serial No. 08/723,686. You may therefore commercialize the invention with the use of the notice "Pat. Pending" if you so desire. The Official Filing Receipt is being retained in our files for safekeeping.

We will keep you advised as to the progress of the application, informing you when we receive the first action on your case from the Patent Office. In the meantime, if we can be of any further assistance, do not hesitate to advise.

Your attention is also called to the fact that if the subject matter of this application is to be validly covered in foreign countries under the provisions of the International Convention, applications must be lodged within one year from the U.S. filing date. We shall be happy to furnish you with additional information and quotations as to the cost of filing corresponding applications in foreign countries upon request.

Very truly yours,

HOVEY, WILLIAMS, TIMMONS & COLLINS

By Warren

Warren N. Williams

WNW:jl

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000.
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Medi-Flex Hospital Products, Inc.	February 3, 2000
TELEPHONE NO. *(Include Area Code)*	FACSIMILE (FAX) Number *(Include Area Code)*
913-451-0880	913-451-8509

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*:
8717 West 110th Street, Suite 750
Overland Park, Kansas 66210

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Beckloff Associates, Inc.
Commerce Plaza II, Suite 720
7400 West 110th Street
Overland Park, Kansas 66210
Telephone: 913-451-3955
Facsimile: 913-451-3846

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 20-832

ESTABLISHED NAME *(e.g. Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Chlorhexidine Gluconate	Chloraprep

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(if any)*	CODE NAME *(if any)*
1,6-di(4-chlorophenyl-diguanido) hexane	

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Solution	2% w/v	Topical

(PROPOSED) INDICATION(S) FOR USE:
Patient Preoperative Skin Preparation

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☒ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION
(check one) ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION
Response to February 20, 1998, FDA Complete Response Letter: Additional Requested Information

PROPOSED MARKETING STATUS (check one) ☐ PRESCRIPTION PRODUCT (Rx) ☒ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1

THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether this site is ready for inspection or, if not, when it will be ready.

Medi-Flex Hospital Products, Inc., 19 Butterfield Trail, El Paso, Texas 79906
Contact: Beckloff Associates, Inc., 913-451-3955

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

	This application contains the following items: *(Check all that apply)*
	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
X	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
X	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	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))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.5 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify)

CERTIFICATION

ree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, autions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. 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.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Michael C. Beckloff	Michael C. Beckloff, President and Chief Executive Officer, Beckloff Associates, Inc.	February 3, 2000

ADDRESS *(Street, City, State, ZIP Code)*	Telephone Number
7400 West 110th Street, Suite 720 Overland Park, Kansas 66210	(913) 451-3955

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FORM FDA 356h (7/97)

Establishment Information
Medi-Flex Hospital Products, Inc.

Corporate Offices:

8717 West 110th Street, Suite 750
Overland Park, Kansas 66210
Telephone: 913-451-0880
Toll Free: 800-523-0502
Telefax: 913-451-8509

Site Functions:

Contact:

Beckloff Associates, Inc.
Commerce Plaza II, Suite 720
7400 West 110th Street
Overland Park, Kansas 66210
Telephone: 913-451-3955
Telefax: 913-451-3846

Manufacturing Facilities:

Establishment Registration Number:

Site Functions:

Contact:

Beckloff Associates, Inc.
Commerce Plaza II, Suite 720
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Overland Park, Kansas 66210
Telephone: 913-451-3955
Telefax: 913-451-3846

Warehouse Facilities:

Site Functions:

Contact:

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Commerce Plaza II, Suite 720
7400 West 110th Street
Overland Park, Kansas 66210
Telephone: 913-451-3955
Telefax: 913-451-3846

Deficiency Summary

1. *There is no study to establish the contribution of each active ingredient (CHG and IPA) to the effect of the product. Specifically, no study contains a CHG alone arm.*

Response:

Two new pivotal clinical studies were designed and conducted in order to evaluate and compare the test drug (2% chlorhexidine gluconate in 70% isopropyl alcohol, CHG + IPA) to an active control (2% aqueous chlorhexidine gluconate, CHG) and reference drug (70% isopropyl alcohol, IPA) for use as a patient preoperative skin preparation as specified in the Tentative Final Monograph for Healthcare Antiseptic Drug Products published in the *Federal Register* on June 17, 1994. The protocols for these studies were submitted to the Agency for review as Protocol Amendments to IND No. (Serial No. 028, June 29, 1999, Protocol No. 990326.MBT; and Serial No. 029, July 26, 1999, Protocol No. 990326.HTR). MicroBioTest, Inc., Sterling, Virginia, performed Protocol No. 990326.MBT and Hill Top Research, Inc., Miamiville, Ohio, performed Protocol No. 990326.HTR. Both of these pivotal clinical studies were conducted using test product in a 3.0-mL swab stick applicator instead of the applicator used previously. The clinical statistical reports for these pivotal studies are included in Volumes 2–12 of this NDA Amendment.

All three test products (CHG + IPA, CHG, and IPA) met the criteria defined in the Tentative Final Monograph for patient preoperative skin preparation in both pivotal studies. A summary of the results for the CHG + IPA test product applied to the abdomen and groin compared to test day baseline for Protocol Nos. 990326.MBT and 990326.HTR is provided below:

CHG + IPA on Abdominal Sites

	Mean Log_{10} Reduction in CFU/cm² from Test Day Baseline		
Protocol Number	**At 10 Minutes**	**At 6 Hours**	**At 24 Hours**
990326.MBT (n=39)	2.56	2.15	2.18
990326.HTR (n=42)	2.52	2.37	2.69

CHG + IPA on Groin Sites

	Mean Log_{10} Reduction in CFU/cm² from Test Day Baseline		
Clinical Site	**At 10 Minutes**	**At 6 Hours**	**At 24 Hours**
990326.MBT (n=36)	4.20	3.50	2.67
990326.HTR (n=26)	3.54	3.74	3.82

In addition, the results from Protocol No. 990326.MBT demonstrated a significantly greater reduction in the CFU/cm² of skin on the groin ten minutes after application of CHG + IPA compared to ten minutes after application of IPA or CHG. The results

from Protocol No. 990326.HTR demonstrated a significantly greater reduction in the CFU/cm^2 of skin on the abdomen 24 hours after application of CHG + IPA compared to the IPA or CHG.

2. *There is no study which establishes the efficacy of the product at a "dry" skin site. Studies have been submitted using forearm, chest, or clavicle sites, but they are flawed by artificial elevation of resident bacteria, small numbers of subjects, or failure to test for the contribution of each active component to the total effect of the product. This is especially important because the testing submitted to date (i.e., with the 24-hour evaluation points) indicates that the product is intended for use in conjunction with peripheral catheters, which are commonly placed at "dry" sites.*

Response:

Protocol Nos. 990326.MBT and 990326.HTR compared the effect of CHG + IPA to its individual components in reducing the mean number of CFU/cm^2 of skin on the abdomen, which is a dry skin site. These studies did not artificially elevate the numbers of bacteria on the skin and did enroll a sufficient number of subjects to demonstrate a significant reduction in CFU/cm^2 of dry skin at the abdominal site. In addition, 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.

<u>Clinical</u>

1. *The following summary lists the principal deficiencies / comments on the clinical efficacy studies submitted in support of this NDA.*

   a. *Studies which did not include either a CHG arm (CXA 1002), or appropriate comparator(s) (CXA 1013); or a vehicle group (CXA1014).*

   Response:

   As stated in the response to Deficiency Summary Item No. 1 above, Protocol Nos. 990326.MBT and 990326.HTR compared the test drug (CHG + IPA) to appropriate comparators (i.e., treatment groups receiving CHG or IPA alone).

   b. *Studies in which bacterial levels were artificially elevated and which did not utilize the CHG / IPA formulation proposed for marketing: CXA 1005, CXA 1007, CXA 1009, and CXA 1010.*

Response:

Bacterial levels were not artificially elevated in Protocol Nos. 990326.MBT and 990326.HTR. In addition, the formulation proposed for marketing (2% [w/v] chlorhexidine gluconate in 70% isopropyl alcohol) was used in both of these new pivotal clinical studies.

c. *Studies which did not include a "dry" test site or CHG alone group: CXA 1020 and CXA 1021.*

Response:

As stated in the response to Deficiency Summary Item No. 2, Protocol Nos. 990326.MBT and 990326.HTR included treatment of the abdomen as a "dry" skin site and CHG alone as one of the three treatment groups.

d. *Studies in which there was no difference between the CHG/IPA formulation and IPA alone or no treatment: CXA 1003, CXA 1011, and CXA 1019.*

Response:

Please refer to the clinical statistical reports for Protocol Nos. 990326.MBT and 990326.HTR included in Volumes 2–12 of this NDA Amendment.

The results from Protocol No. 990326.MBT demonstrated a significantly greater reduction in the CFU/cm^2 of skin on the groin ten minutes after application of CHG + IPA compared to ten minutes after application of IPA ($p = 0.0096$) or CHG ($p = 0.0057$).

The results from Protocol No. 990326.HTR demonstrated a significantly greater reduction in the CFU/cm^2 of skin on the abdomen 24 hours after application of CHG + IPA compared to the IPA ($p = 0.0022$) or CHG ($p = 0.0272$).

2. *Regarding the clinical simulation study (CXA 1021) that was submitted in partial fulfillment of the requirements for skin prepping prior to injection and to demonstrate persistent effect, the deficiencies are as follows:*

a. *Four adjacent regions were used as test sites on the inguinal region test subjects (Addendum V; [redacted] February 17, 1997, Protocol No. 970101.01). Since the test and vehicle products were randomized to site but not randomized to region, data should be provided which demonstrate that*

the bacterial populations are not statistically different between regions 1 and 4 of test subjects at baseline.

Response:

As stated previously, two new pivotal clinical studies, Protocol Nos. 990326.MBT and 990326.HTR, were conducted to evaluate Chlorhexidine Gluconate 2% (w/v) Topical Solution for the indication of "patient preoperative skin preparation." In these studies, a computer-generated randomization schedule was used to randomize all three study drugs to treatment areas on the abdomen and groin (inguinal). Another computer-generated randomization schedule was used to randomize sample times to sampling sites within the treatment areas.

b. *In the Final Study Report #970101 (August 8, 1997, submission), compliance with the randomization scheme (Appendix IV of Addendum 1) was assessed. Eight of the twenty-two subjects (36%) did not receive assignments as defined by the randomization scheme. Thus, the results of the study may have been influenced by this nonrandomization and may have an inherent bias. Please explain.*

Response:

As stated previously, two new pivotal clinical studies, Protocol Nos. 990326.MBT and 990326.HTR, were conducted to evaluate Chlorhexidine Gluconate 2% (w/v) Topical Solution for the indication of "patient preoperative skin preparation." In these studies, all subjects were screened for CFU/cm^2 of skin on the abdomen and groin prior to enrollment in the studies. All subjects who met the entry criterion for minimum number of CFU/cm^2 of skin on the abdomen and groin during the screening test were enrolled in the studies and randomized to treatment on the abdomen and/or groin with two of the three test products to eliminate bias.

c. *Complete data sets for each test subject were not provided in Addendum II of the report. All raw data should be provided up until departure of the test subject from the study. The primary focus should be on subjects 10, 15, and 26. Please submit these data.*

Response:

Please refer to the Amendment to the Clinical Section of the NDA submitted to the Agency on August 8, 1997, for complete data sets for all subjects in CXA 1021 (Protocol No. 970101.01). Complete data sets for Subject Nos. 10, 15, and 26 are provided on pages 91-98, 123-130, and 227-234 of the August 1997 NDA Amendment.

3. *In any resubmission of this application, information / data must be presented which establish(es) the safety of such use, given that the irritancy and sensitization testing suggest that the product would be unacceptable to the patient when used under occlusion. Specifically, the resubmission should discuss the possibilities for sensitization and / or irritancy reactions under the proposed conditions of use*

Response:

Protocol Nos. 990326.MBT and 990326.HTR assessed skin irritation at the site of drug application before and 10 minutes, 6 hours, and 24 hours after application of the three test drugs. A Tegaderm™ dressing covered all treatment sites for 24 hours after topical application of the three test drugs. No clinically significant, drug-related skin irritation was observed on any test site treated with CHG + IPA, CHG, or IPA in these studies. Occasional mild skin irritation associated with the Tegaderm™ dressing was observed.

As stated previously, the indication for this NDA has been revised to "patient preoperative skin preparation." Thus, the comments regarding are no longer applicable.

4. *If the care indications are still desired, any new pivotal stud(ies) submitted should closely follow the outline*

Response:

As stated previously, the indication for this NDA was officially changed to "patient preoperative skin preparation," and Protocol Nos. 990326.MBT and 990326.HTR were designed specifically to assess the efficacy and safety of Chlorhexidine Gluconate 2% (w/v) Topical Solution for this indication.

5. *If any of the indications specified in the Tentative Final Monograph (TFM) for Health Care Antiseptic Drug Products (health-care personnel hand wash, surgical scrub, patient preoperative skin preparation) are desired, the test methodology specified in the TFM for the selected indication should be used.*

Response:

Protocol Nos. 990326.MBT and 990326.HTR were designed specifically to evaluate Chlorhexidine Gluconate 2% (w/v) Topical Solution for the indication of "patient preoperative skin preparation," and the methodologies specified in the TFM for that indication were followed in these studies.

[redacted]

Microbiology

1. *The requirements described in the TFM for Health Care Antiseptic Drug Products regarding the studies needed to support the in vitro spectrum of activity for this product have not been met. The information provided is insufficient since it represents a single MIC value for a single species tested. In addition, it is not clear whether the MIC studies were conducted according to established methods in the TFM. The in vitro MIC studies as described in the TFM must be performed. The following modifications regarding the number of strains that should be tested can be made: (1) for the active ingredient (CHG alone) study, 10 strains of each species listed in the TFM should be tested (i.e., a reduction from the required 50 strains for each species); (2) the product, Chloraprep, should be tested with 50 strains of the listed nosocomial pathogens at a central laboratory experienced in the performance of MIC studies using the NCCLS protocols; and (3) the vehicle (70% IPA) requires no further testing.*

Response:

A new in vitro study (Protocol No. CMI 98-13R) was performed and previously submitted to the FDA as an Amendment to NDA No. 20-832 on April 1, 1999. In this study, the antimicrobial spectrum of a 2% CHG in 70% IPA, a 2% aqueous CHG solution, a 4% CHG solution, a povidone iodine solution, and a 70% IPA solution were compared. This study was performed by an experienced central laboratory [redacted] using an NCCLS broth microdilution method to determine the minimum inhibitory concentration (MIC) of 1175 microbial isolates. This new in vitro study meets all requirements described in the TFM for Healthcare Antiseptic Drug Products to support the in vitro spectrum of activity of

Chlorhexidine Gluconate 2% (w/v) Topical Solution (2% chlorhexidine gluconate in 70% isopropyl alcohol).

2. *Validation of the neutralization system for the in vitro microbiology studies (MICs and time-kill kinetics) and the in vivo clinical simulation study could not be evaluated. The written presentation of the neutralizer validation studies should be consistent in content and format with those used to publish scientific articles. Thus, the report should contain an introduction which describes the purpose of the study, the material and methods used to perform the study, the results and raw data, the statistical methods used to analyze the data and the conclusions. The introduction and the conclusions should provide reference to the published literature in the development and support of the results and conclusions described in each study.*

Response:

The new in vitro MIC study report for Protocol No. CMI98-13R was written to be consistent in content and format with the requirements for publication in the *Journal of Clinical Microbiology*. It contains the following sections: Abstract, Introduction, Materials and Methods (with subsections for Microorganisms, Test Agents, Test Procedures, and Quality Control), Results, and Discussion. The microdilution method used in this study conformed to NCCLS guidelines.

In the new pivotal clinical studies, Protocol Nos. 990326.MBT and 990326.HTR, a neutralization study was performed at each site in accordance with the site's internal SOP in order to assure the validity of the neutralizers used in the recovery medium. The results of the neutralization study are included as an Appendix in each clinical statistical report.

3. *In general, the presentation of the data, the analysis of the data, and conclusions were provided in a manner that made evaluation difficult. It is recommended that all future reports be presented in a format suitable for publication in a journal (e.g., journals published by the American Society for Microbiology). Thus, the reports should include an abstract which summarizes the findings of the study as well as the specific items listed in #2 above. The discussion should include evidence from the published literature (if any) which supports the conclusions of the study submitted to the FDA.*

Response:

Please refer to the response provided in Microbiology, Item No. 2.

Chemistry/Microbiology

Your commitment to revise the specifications for applicators containing chlorhexidine gluconate 2% (w/v) is noted.

Response:

Residual limits specifications have been revised to and 3.0-mL swab stick applicators containing Chlorhexidine Gluconate 2% (w/v) Topical Solution.

Labeling

Response:

The proposed labeling for Chlorhexidine Gluconate 2% (w/v) Topical Solution has been revised and is included in Appendix 1. Please note that this statement has been removed from the revised proposed labeling.

2. *Submit revised draft labeling (see attached prototype for reference if an OTC use is established) in accordance with:*

   a. *Proposed rule for OTC healthcare antiseptic drug products published in the* Federal Register *of June 17, 1994 (59 FR 31402)*

   b. *Proposed rule for OTC format and content requirements for OTC drug product labeling published in the* Federal Register *of February 27, 1997 (62 FR 9024 at 9050).*

   Response:

   The labeling for Chlorhexidine Gluconate 2% (w/v) Topical Solution has been revised in accordance with the proposed rule for OTC health-care antiseptic drug products published in the *Federal Register* of June 17, 1994, (59 FR 31402) and the proposed rule for OTC format and content requirements for OTC drug product labeling published in the *Federal Register* of February 27, 1997, (62 FR 9024 to 9050). The revised proposed labeling is included in Appendix 1.

3. *Revise the immediate container labels to contain the name of the manufacturer in typewritten text, not logo.*

Response:

The immediate container labels have been revised to contain the name of the manufacturer (Medi-Flex Hospital Products, Inc.) in typewritten text. The immediate container label is provided in Appendix 2.

4. *Provide draft labeling in color mock-up form for all labeling (primary packaging, carton, reformatted package insert) for both the* [redacted]

Response:

Draft labeling in color mock-up form is provided for all labeling (package insert, primary packaging, intermediate packaging, outer shipper packaging) for the 3.0-mL applicator containing Chlorhexidine Gluconate 2% (w/v) Topical Solution in Appendices 1–4, respectively.

5. *Explain the discrepancy between statements made in the* [redacted] *package insert and in the Standard Operating Procedure (S.O.P.) for packaging* [redacted]

Response:

Only cartons containing twenty-five (25) 3.0-mL applicators containing Chlorhexidine Gluconate 2% (w/v) Topical Solution will be commercially distributed.

6. *If two (or more) carton sizes are desired, labeling must be submitted for each.*

Response:

Only cartons containing twenty-five (25) 3.0-mL applicators containing Chlorhexidine Gluconate 2% (w/v) Topical Solution will be commercially distributed.

7. *Provide the packaging S.O.P. for the* [redacted]

Response:

The packaging SOP for the 3.0-mL applicators containing Chlorhexidine Gluconate 2% (w/v) Topical Solution is included in Appendix 5.