

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**21-555**

**Administrative/Correspondence**

**Division Director's Memorandum**  
**NDA 21-555 ChloroPrep One-Step Sepp® Applicator**  
**October 3, 2002**

ChloroPrep One Step®(chlorhexidine gluconate 2% w/w and isopropyl alcohol [IPA] 70% w/v) was a new drug application (NDA) approved in July, 2000, as a patient *preoperative* skin preparation. The package contained 3 mL of ChloroPrep solution in a sponge applicator. In this original NDA, the drug product was tested in two adequate and well-controlled studies to support a patient preop indication. The control used for both studies was 70% isopropyl alcohol.

In December, 2001, the same Applicant (Medi-Flex Hospital Products) submitted another application to the Agency consisting of the same drug product, ChloroPrep, in a new packaging configuration called a "Sepp" applicator. The Sepp applicator consists of 0.67 mL Chloroprep solution in a sealed glass ampule. The glass ampule is placed within a plastic tube, sealed at one end, with a — applicator tip at the other end. To use the product, one breaks the glass ampule within the plastic tube, and drug product flows onto the applicator tip.

The Sepp submission was filed for a new indication – patient *pre-injection* skin preparation – as well as patient preoperative skin prep. The Sepp submission consists of a detailed description of the device and a patient preoperative skin preparation study that follows the procedure in the Tentative Final Monograph (TFM) for Health Care Antiseptics. This study includes evaluation of the product both as a patient preop skin prep and as a preinjection skin preparation. The study does not have a concurrent control group. In general, the Division recommends that preop skin prep and preop surgical prep studies be conducted with a concurrent control. In the case of this NDA, however, the trial data can be viewed as providing substantial evidence of efficacy for the following reasons:

- 70% IPA is approved in the TFM antiseptic monograph as a patient preop, and thus is an acceptable control product. Chlorhexidine gluconate is included in the formulation to provide greater residual activity than IPA alone, and the original studies established the efficacy of the combination. Thus, the data in the original NDA establish that the product easily meets the standards for preops as outlined in the Monograph.
- The new drug application with the Sepp configuration can be viewed as a "new dosage form" of ChloroPrep, essentially seeking a line extension - pre-injection. The controlled studies of the original NDA provide corroborative evidence (essentially as historical controls) to support the data of the Sepp application.
- The absence of a concurrent control group and use of historical controls is acceptable, given the consistent magnitude of the decrease in colony counts seen with this drug product (1 log<sub>10</sub> per cm<sup>2</sup> for pre-injection sites and up to 3 log<sub>10</sub> per cm<sup>2</sup> for pre-operative sites; the latter is consistent with the results seen in the 3 mL application), use of the same ingredients in the One Step 3 mL and Sepp formulations, and use of the same manufacturing process for both drug products.

In conclusion, the applicant has provided substantial evidence to support approval of ChloroPrep using a new product configuration called Chloro-Prep One-Step Sepp® Applicator. This decision is based on review of the totality of the evidence compiled by the applicant for the ChloroPrep One Step products.

Janice M. Soreth, M.D.

Division of Anti-Infective Drug Products

## NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-555	Efficacy Supplement Type SE-	Supplement Number
Drug: Chloraprep® One Step Sepp® Applicator		Applicant: Medi-Flex Hospital Products
RPM: Tia Frazier/Maureen Dillon-Parker		HFD- 560/520      Phone # 72222/72125
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name): NDA 20-832 Chloraprep® One-Step
❖ Application Classifications:		
• Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
• Chem class (NDAs only)		Type 3 – Topical Antiseptic
• Other (e.g., orphan, OTC)		OTC professional use
❖ User Fee Goal Dates		
❖ Special programs (indicate all that apply)		
		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review
❖ User Fee Information		
• User Fee		<input checked="" type="checkbox"/> Paid
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Exception for review (Center Director's memo)		
• OC clearance for approval		
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.		
		<input checked="" type="checkbox"/> Verified
❖ Patent		
• Information: Verify that patent information was submitted		<input checked="" type="checkbox"/> Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV  21 CFR 314.50(i)(1)

	<input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).</li> </ul>	<input type="checkbox"/> Verified
Exclusivity (approvals only)	
<ul style="list-style-type: none"> <li>Exclusivity summary</li> </ul>	Enclosed
<ul style="list-style-type: none"> <li>Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!</li> </ul>	<input type="checkbox"/> Yes, Application # _____ <input checked="" type="checkbox"/> No
Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	
<b>General Information</b>	
Actions	
<ul style="list-style-type: none"> <li>Proposed action</li> </ul>	<input type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA
<ul style="list-style-type: none"> <li>Previous actions (specify type and date for each action taken)</li> </ul>	**AP 7/14/2002; NA 2/20/98 for NDA 20-832 Chloraprep One-Step 3mL. No previous actions for this NDA.
<ul style="list-style-type: none"> <li>Status of advertising (approvals only)</li> </ul>	<input checked="" type="checkbox"/> Materials requested in AP letter <input type="checkbox"/> Reviewed for Subpart H
Public communications	
<ul style="list-style-type: none"> <li>Press Office notified of action (approval only)</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> Not applicable
<ul style="list-style-type: none"> <li>Indicate what types (if any) of information dissemination are anticipated</li> </ul>	<input checked="" type="checkbox"/> None <input type="checkbox"/> Press Release <input type="checkbox"/> Talk Paper <input type="checkbox"/> Dear Health Care Professional Letter
Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
<ul style="list-style-type: none"> <li>Division's proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	Enclosed
<ul style="list-style-type: none"> <li>Most recent applicant-proposed labeling</li> </ul>	Enclosed
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	Enclosed
<ul style="list-style-type: none"> <li>Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings (indicate dates of reviews and meetings)</li> </ul>	OTC labeling
<ul style="list-style-type: none"> <li>Other relevant labeling (e.g., most recent 3 in class, class labeling)</li> </ul>	Enclosed

Labels (immediate container & carton labels)	
Division proposed (only if generated after latest applicant submission)	
Applicant proposed	Enclosed
Reviews	Not applicable
Marketing commitments	None
Agency request for post-marketing commitments	None
Documentation of discussions and/or agreements relating to post-marketing commitments	None
Outgoing correspondence (i.e., letters, E-mails, faxes)	Enclosed
Memoranda and Telecons	Enclosed
Types of Meetings	
EOP2 meeting (indicate date)	None held
Pre-NDA meeting (indicate date)	None held
Pre-Approval Safety Conference (indicate date; approvals only)	None held
Other	None
Priority Committee Meeting	
Date of Meeting	Not applicable
48-hour alert	Not applicable
Public Register Notices, DESI documents, NAS, NRC (if any are applicable)	None
<b>Summary Application Review</b>	
Summary Reviews (e.g., Office Director, Division Director, Medical Team) (indicate date for each review)	Anti-Infectives Division Division Director Memo
<b>Clinical Information</b>	
Initial review(s) (indicate date for each review)	(1) 7/29/02
Biopharmaceutical (efficacy) review(s) (indicate date for each review)	(1) 9/25/02
Update review(s) (indicate date or location if incorporated in review)	(1) 5/9/02
Public Page (separate page for each indication addressing status of all age groups)	(1) 10/3/02
Biopharmaceutical Worksheet (NME approvals only)	Not an NME
Biopharmaceutical review(s) (indicate date for each review)	(1) 8/22/02
Pharmaceutical review(s) (indicate date for each review)	N/A
Biopharmaceutical Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
Inspection Review Summary (DSI)	
Clinical studies	No Inspections Requested
Biopharmaceutical Bioequivalence studies	N/A

<b>CMC Information</b>	
❖ CMC review(s) ( <i>indicate date for each review</i> )	(1) CMC
❖ Environmental Assessment	
• Categorical Exclusion ( <i>indicate review date</i> )	See chemistry review
• Review & FONSI ( <i>indicate date of review</i> )	See chemistry review
• Review & Environmental Impact Statement ( <i>indicate date of each review</i> )	See chemistry review
❖ Micro (validation of sterilization & product sterility) review(s) ( <i>indicate date for each review</i> )	(1) 10/2/02
❖ Facilities inspection (provide EER report)	Date completed: ( ) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested ( ) Not yet requested
<b>Nonclinical Pharm/Tox Information</b>	
❖ Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	Refer to IND review for 46,243 dated 8/18/99
❖ Nonclinical inspection review summary	NA
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	No carcinogenicity studies requested or submitted.
❖ CAC/ECAC report	NA

10/3/02

APPEARS THIS WAY  
ON ORIGINAL

EXCLUSIVITY SUMMARY for NDA # 21-555 SUPPL # NA  
Trade Name ChloraPrep One-Step Sepp Applicator  
Generic Name Chlorhexidine Gluconate 2%/isopropyl alcohol 70%  
(v/v)  
Applicant Name Beckloff Associates, Inc./Medi-flex Hospital  
Products, Inc.  
HFD-520/560  
Approval Date October 7, 2002

**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.

NA

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:

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?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /\_\_\_/ NO /\_x\_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /\_\_\_/ NO /\_x\_/

If yes, NDA # \_\_\_\_\_ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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 9 (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 /\_\_\_/

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 # 20-832 \_\_\_\_\_ Chloraprep

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. 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 9.

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 9:

- (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 # 990622. —

Investigation #2, Study #

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 /\_\_\_/

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 /\_\_\_/

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 # 990622.

Investigation # \_\_, Study #

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 # 46,243 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 / \_\_\_ / 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/

\_\_\_\_\_  
Signature of Preparer  
Date

/S/

\_\_\_\_\_  
Signature of Office or Division  
Date \_\_\_\_\_

cc:  
Archival NDA  
HFD-520/Division File  
HFD-560/Division File  
HFD-520/RPM/Dillon-Parker  
HFD-560/RPM/Frazier  
HFD-093/Mary Ann Holovac  
HFD-104/PEDS/T.Crescenzi

Form OGD-011347  
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

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Janice Soreth  
10/17/02 04:40:22 PM

Charles Ganley  
10/17/02 03:22:17 PM

**PEDIATRIC PAGE**

(Complete for all APPROVED original applications and efficacy supplements)

DA/BLA #: 21-555 Supplement Type (e.g. SE5): \_\_\_\_\_ Supplement Number: \_\_\_\_\_

Stamp Date: December 10, 2001 Action Date: \_\_\_\_\_

HFD-520/560 Trade and generic names/dosage form: ChlorPrep One-Step Sepp Applicator (chlorhexidine gluconate 2% w/w and isopropyl alcohol 70% w/v).

Applicant: Medi-Flex Hospital Products, Inc. Therapeutic Class: 3S

Indication(s) previously approved: Patient preoperative skin preparation (NDA 20-832)

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 2

Indication #1: Patient preoperative skin preparation

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply:  Partial Waiver  Deferred  Completed  
NOTE: More than one may apply  
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Indication #2: Patient preinjection skin preparation

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply:  Partial Waiver  Deferred  Completed  
NOTE: More than one may apply  
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

**Section A: Fully Waived Studies**

**For Indication #1:**

**Reason(s) for full waiver:**

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: \_\_\_\_\_

Note: This product is labeled for children 2 months of age and older (refer to review of original NDA 20-832). It is felt that the product is too irritating to test in children younger than 2 months.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section B: Partially Waived Studies**

Age/weight range being partially waived:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section C: Deferred Studies**

Age/weight range being deferred:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): \_\_\_\_\_

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section D: Completed Studies**

Age/weight range of completed studies:

NDA 21-555

Page 3

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Comments:

*If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

This page was completed by:

*{See appended electronic signature page}*

~~\_\_\_\_\_~~  
David C. Bostwick, Clinical Reviewer

cc: NDA

HFD-950/ Terrie Crescenzi

HFD-960/Grace Carmouze

(revised 9-24-02)

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960  
301-594-7337**

**Attachment A**

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: Patient Preinjection skin preparation

Is there a full waiver for this indication (check one)?

**Yes: Please proceed to Section A.**

**No: Please check all that apply:      Partial Waiver      Deferred      Completed**

**NOTE: More than one may apply**

**Please proceed to Section B, Section C, and/or Section D and complete as necessary.**

**Section A: Fully Waived Studies**

Reason(s) for full waiver:

**Products in this class for this indication have been studied/labeled for pediatric population**

**Disease/condition does not exist in children**

**Too few children with disease to study**

**There are safety concerns**

**Other: \_\_\_\_\_**

Note: This indication is included in the larger patient preoperative skin preparation indication described above.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section B: Partially Waived Studies**

Age/weight range being partially waived:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for partial waiver:

**Products in this class for this indication have been studied/labeled for pediatric population**

**Disease/condition does not exist in children**

**Too few children with disease to study**

**There are safety concerns**

**Adult studies ready for approval**

**Formulation needed**

**Other: \_\_\_\_\_**

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section C: Deferred Studies**

Age/weight range being deferred:

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): \_\_\_\_\_

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section D: Completed Studies**

Age/weight range of completed studies:

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Comments:

*If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.*

This page was completed by:

*{See appended electronic signature page}*

\_\_\_\_\_  
 David Bostwick, Clinical Reviewer

cc: NDA  
 HFD-960/ Terrie Crescenzi  
 (revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960  
 1-594-7337

Note: NDA 20-832 Supplement-003 provided for a new indication and a new delivery system/dosage form. This application became a new NDA in August, 2002, and was assigned NDA number 21-555.

## MEMORANDUM OF TELECON

DATE: October 3, 2002

APPLICATION NUMBER: NDA 21-555, Chloraprep One Step Sepp Applicator (2% chlorhexidine gluconate) swab

BETWEEN:

Name: Diane Beatty, Vice President  
Phone: (913) 451-3955  
Representing: Beckloff Associates, Inc. and Medi-flex Hospital Products, Inc.

AND

Name: Tia Frazier, Regulatory Project Manager  
Michael Benson, Regulatory Review Pharmacist  
Debbie Lumpkins, Team Leader  
Division of Over-the-Counter Drug Products, HFD-560

SUBJECT: Labeling negotiation teleconference

FDA clarified the regulations concerning Drug Facts Labeling requirements for the *Warnings* labeling section.

The sponsor agreed to the following labeling revisions:

1. Under *Directions*, revise the uppercase "d" to be a lowercase "d".
2. Under *Warnings*:
  - a. remove the bullets
  - b. indent and vertically align statements

The conversation concluded cordially, with a commitment from from the sponsor to submit identical copies of the proposed labeling electronically, via facsimile, and as an amendment to NDA 21-555.

/s/

---

Debbie Lumpkins  
Team Leader

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/  
-----

Tia Frazier  
10/3/02 06:19:24 PM  
CSO

Debbie Lumpkins  
10/4/02 07:43:35 AM  
INTERDISCIPLINARY



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation V

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**FACSIMILE TRANSMITTAL SHEET**

---

**DATE:** September 26, 2002

<b>To:</b> Diane Beatty	<b>From:</b> Tia Frazier
<b>Company:</b> Beckloff Associates, Inc.	Division of Division of Over-the-Counter Drug Products
<b>Fax number:</b> (913) 451-8509 (913) 451-3846 alternate	<b>Fax number:</b> (301) 827-2315
<b>Phone number:</b> (913) 451-3846	<b>Phone number:</b> 301-827-2271
<b>Subject:</b> Discipline Review Completed for NDA 21-555 Labeling Section	

**Total no. of pages including cover:** 3

---

**Comments:**

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

---

**Document to be mailed:**                       YES                       NO

---

**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.**

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-2222. Thank you.

Before these carton and individual lid applicator labels can be approved, you must make changes in Drug Facts labeling as outlined, below.

In terms of timing of your response to this information request, we remind you that we intend to review and act on this new drug application, with or without an amendment, on or before October 12, 2002. We may defer the review of any amendments to the application that are received too close to the October 12 action deadline.

A. Carton Label

"Drug Facts" Back Panel

1. Under *Warnings*,

(a). bold "Flammable" and "For external use."

(b) vertically align bulleted statements under *Do not use*.

2. In *Directions*, revise the statement [

] to read "The maximum treatment area for one applicator is approximately 2.5 by 2.5 inches." Additionally, move the same statement to the *Use* section immediately after the word "injection". Health care personnel are more likely see the maximum area treatable with one applicator sooner under *Use*, rather than under *Directions*.

3. Under *Questions*, debold "Call" and "(8 a.m.-5 p.m. CST)"

Additionally, we make the following recommendations to enhance your labeling:

4. Include the directions "Pinch the barrel of the applicator to break the ampule and release the antiseptic. Do not touch the applicator tip. Press the applicator tip against treatment area until liquid is visible on the skin" on your applicator label.

5. Resubmit draft revised labels for our review and comment.

APPEARS THIS WAY  
ON ORIGINAL

2 pages redacted from this section of  
the approval package consisted of draft labeling

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

-----  
Marina Chang  
9/26/02 08:33:57 AM

Revised Drug Facts Labeling (DFL) for the  
carton submitted (via facsimile)  
October 3, 2002. FDA approved this  
submitted draft DFL.

Final Label

# Beckloff Associates, Inc.

Pharmaceutical Research and Development



Commerce Plaza II, Suite 720 • 7400 West 110th Street

Overland Park, Kansas 66204

Telephone 913-451-3955 • Facsimile 913-451-3846 • email: bschlenk@beckloff.com

## FACSIMILE TRANSMISSION

**TO:** Ms. Tia M. Frazier  
 Food and Drug Administration

**FAX No:** 301-827-2315

**DATE:** October 3, 2002

**FROM:** Brenda C. Schlenk, R.Ph.

**cc:** Ms. M. Dillon-Parker; FDA  
 301-827-2325  
 Ms. C. Crosby; Medi-Flex  
 451-8509 (cover only)

**TOTAL NUMBER OF PAGES INCLUDING THIS NOTICE:** 13

**Subject:** Amendment to Pending Application Regarding NDA No. 21-555, Chlorhexidine Gluconate 2% (w/v) Topical Solution in the Sepp Applicator

Per your request, included is Amendment No. 004 to NDA No. 21-555 containing labeling revisions regarding Chlorhexidine Gluconate 2% (w/v) Topical Solution in the Sepp Applicator.

Please be advised that an archival copy has been submitted to the NDA.

Best regards,

BCS

BCS:ffw

Enclosure

**Best Possible Copy**

The information contained in this facsimile is CONFIDENTIAL and is intended only for use by the individual(s) and/or entity(s) to whom addressed. Copying or distributing this transmission is strictly prohibited except by the intended recipient, or their employee, or agent. If this communication is received in error, please notify us immediately by telephone.

1 pages redacted from this section of  
the approval package consisted of draft labeling

Revised immediate container labeling submitted (via facsimile) on October 3, 2002. FDA is approving this submitted draft container labeling.

**B. Individual Lidding Applicator Label**

**ChloroPrep®  
Sepp**  
Chlorhexidine  
Gluconate 2% w/v;  
70% Isopropyl  
Alcohol v/v  
0.67-mL Applicator

**Warning.  
Flammable.  
Keep away from  
fire or flame.  
Do not use with  
electrocautery  
procedures.  
Applicator sterile  
unless seal is  
broken.**

**Medi-Flex, Inc.  
Overland Park, KS**

**Lot No:  
Exp.:**

4 pages redacted from this section of  
the approval package consisted of draft labeling

Note: NDA 20-832 Supplement-003 provided for a new indication and a new delivery system/dosage form. This application became a new NDA in August, 2002, and was assigned NDA number 21-555.



b7c 2155

NDA 20-832\S-003

**INFORMATION REQUEST LETTER**

Beckloff Associates, Inc.  
Attention: Michael Beckloff  
President and Executive Officer  
7400 West 110<sup>th</sup> St., Suite 720  
Overland Park, Kansas 66210

Dear Mr. Beckloff:

Please refer to your December 10, 2001, supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Chloraprep (2% chlorhexidine gluconate) topical solution.

We also refer to your submissions dated April 19, and May 6, 2002.

We are reviewing the microbiology section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Provide an assessment of the maximum tolerated concentration (MTC) of neutralizer for the target pathogens, as specified in the ASTM method. In your submission, you state that the neutralizer effectiveness protocol followed the standard operating procedure described as 1009.10(1) Option III, and the recommendations set forth by ASTM standard E1054-91, "Standard Practices for Evaluating Inactivation of the Antimicrobial Agents Used in Disinfectant, Sanitizer, Antiseptics or Reserved Products."
2. Justify the volume of antiseptic used in the validation of the neutralizer and address the following questions and comments:
  - a. Why was one milliliter of ChloraPrep One-Step used to validate the neutralizer?
  - b. Justify the relationship of this volume (1cc) and that found in the clinical simulation study samples. Your prior test laboratories have performed the validation of the neutralization by obtaining 10 independent preoperative skin preparation samples, pooling them to reflect an average concentration of CHG in a sample, and then used an appropriate volume to validate the neutralizer. This procedure needs to be carried out for this study.
3. Provide precision and interpretation of the data by transformation to square root values and *t* test analysis, as required by the ASTM method.

4. Provide an assessment of the maximum tolerated concentration (MTC) of neutralizer for the targeted pathogens, as required under the ASTM method.

If you have any questions, call Tia Frazier, Project Manager, at 301-827-2271.

Sincerely,

*{See ~~appended~~ electronic signature page}*

David Hilfiker, M.S.  
Chief, Project Management Staff  
Division of Over-the-Counter Drug Products  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

-----  
David Hilfiker  
6/26/02 01:21:33 PM



Michael C. Beckloff  
President and Chief Executive Officer  
Beckloff Associates, Inc.  
Agent for Mediflex Hospital Products, Inc.  
7400 West 110th Street  
Overland Park, Kansas 66210

AUG 16 2002

## Invoice Enclosed

**RE: Application fee for NDA 20-832, ChloroPrep  
(chlorhexidine gluconate), Supplement 003**

Dear Mr. Beckloff:

This communication includes an invoice (Attachment A) for an application fee under the user fee provisions of the Federal Food, Drug, and Cosmetic Act (the Act)<sup>1</sup> for NDA 20-832 ChloroPrep (chlorhexidine gluconate). This communication also responds to your letter of April 18, 2002, to Michael Jones of the Center for Drug Evaluation and Research.

### I. Background Information for Supplement 003

The Division of Over-the-Counter Drug Products received a supplement (S-003) to NDA 20-832 on December 12, 2001, for the use of an additional applicator, called a Sepp, for chlorhexadine gluconate 2% w/v for the approved indication of patient preoperative skin preparation and for a new indication of patient preinjection skin preparation. Mediflex Hospital Products, Inc. (Mediflex), submitted the supplement and paid the fiscal year (FY) 2001 fee for a supplement that requires clinical data for approval.

### II. What is FDA's Policy on Submitting an NDA Versus a Supplement?

Agency policy is expressed in the guidance for industry on *Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees* (December 2000)<sup>2</sup>(bundling policy). The bundling policy states that:

Different dosage forms (Orange Book, Appendix C) should be submitted in separate original applications unless the products are identical (drugs) or alike (biological products) in quantitative and qualitative composition

<sup>1</sup> Section 736(a)(1), 21, U.S.C. 379h(a)(1)

<sup>2</sup> Available on the Internet at [www.fda.gov/cder/pdofa/default.htm](http://www.fda.gov/cder/pdofa/default.htm) under Guidelines.

(e.g., a sterile liquid in a single dose vial that is intended for use as either an injectable or an inhalation solution).

### III. Should Mediflex Submit an NDA or a Supplement for the Sepp?

#### A. What are the definitions of swab and sponge?

As noted above, FDA's Orange Book (*Approved Drug Products with Therapeutic Equivalence Evaluations*), Appendix C, lists the different dosage forms. The list includes, among many other dosage forms, *swab* and *sponge*. CDER's Data Standards Manual<sup>3</sup> defines a sponge as "an absorbent pad of folded gauze or cotton." A swab is defined as "a wad of absorbent material usually wound around one end of a small stick and used for applying medication or for removing material from an area."

#### B. What is the dosage form approved under NDA 20-832?

##### 1. What was originally submitted under NDA 20-832?

There were two products included in the original application submitted in 1997. One of the products was called a *Frepp* and the other was called a *Sepp*.

The Sepp is described in the original application as "similar to an antiseptic *swab stick*, but with the solution held in a glass ampule configuration, having rounded seals at both ends" which has at one end "an applicator tip of formed and bonded to the plastic tube." (Emphasis added).

The original application describes the Frepp as follows:

The Frepp container closure is a functionally identical glass crush ampule containing 1.1 mL of formulation with the ampule enclosed in a molded plastic housing sealed on one length with a within an outer *fabric sponge*. At the time of use, the glass ampule is crushed by finger tip compression of the molded plastic housing. Glass is filtered by the and released solution exits the full length of the plastic housing through the broad surfaced *applicator sponge*.

(Emphasis added.)

The Sepp and the Frepp were further described in your U.S. Patent Application with assigned Serial No. 08/723,686 as follows:

In one embodiment of the invention, a cylindrical glass ampule is housed within a tubular, flexible cover which has a *porous applicator swab* at one end thereof. Upon crushing of the glass ampule,

<sup>3</sup> CDER's Data Standards Manual on dosage forms can be found on the Internet at <http://www.fda.gov/cder/dsm/DRG/drg00201.htm>.

the CHG released therefrom impregnates the *swab* allowing the user to spread the CHG across an area to be sanitized. In a second embodiment of the invention, a cylindrical glass ampule is received within a semi-cylindrical, open-sided body cover having a flange portion that mounts a *sponge-like swab* communicating with the interior of the body cover. Opposed integral wing-like gripping members on the ampule permit the user to crush the ampule by squeezing the members toward one another whereupon the CHG is released from the ampule and impregnates the *sponge swab*.

(Emphasis added.)

## 2. What was approved under the original application?

The two products, the Frepp and Sepp, discussed above were reviewed under the original submission and a not approvable letter was issued February 20, 1998. In your March 16, 2000, response to the not approvable letter, you provided a chemistry amendment that described a new 3 mL applicator, which was ultimately approved.

Your March 2000 submission describes the new 3 mL product as follows:

The applicator consists of a glass ampoule containing 3 mL of solution enclosed in a molded plastic tube sealed on one end with a cap and an outer sponge (medical grade). ... The released solution exits the full length of the plastic housing into the broad-surfaced *applicator sponge* which is made up of (pore size: )

(Emphasis added.)

We also noted that the front panel of the box that contains 25 applicators states that the contents are "1 Each Sponge, Latex Free." Further, your web site<sup>4</sup> describes ChloroPrep as follows:

No bottles to open. *No swabs* to drip. No mess. No stain. It's that simple.

(Emphasis added.)

The directions on your web site for ChloroPrep state:

Simply pinch the wings on the applicator to break the ampule and release the ChloroPrep antiseptic into the *sponge pad*. It is important not to touch the pad.

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<sup>4</sup> www.chloroprep.com

Gently press the *sponge* against the treatment area until liquid is visible on the skin ....

(Emphasis added.)

It is clear from our examination of the samples provided, from the information noted above, from the application, and from your web site, that the product approved under NDA 20-832 is a sponge and not a swab. It fits CDER's definition of a sponge, and your approved product is noted as a sponge in CDER's Orange Book.

**C. What dosage form did you submit in supplement 003?**

Supplement 003 reintroduces the Sepp that was submitted in the original application. Your December 2001 submission described the Sepp as being similar to an antiseptic swab stick. We also refer you to the discussion above, in which the patent described the product as a porous applicator swab. The information submitted in the original application and the information submitted in the new supplement clearly show that the Frepp meets CDER's definition of a swab.

**D. Was supplement 003 appropriately submitted? Was the appropriate fee paid?**

The dosage form submitted and approved in your application for ChloroPrep (NDA 20-832) is considered a sponge. The product you submitted in S-003 is considered a swab.<sup>5</sup> Because these two products are different dosage forms, a new NDA should have been submitted instead of supplement 003 in accordance with Agency policy as expressed in the bundling policy. Because an NDA should have been submitted, the FY 2002 fee paid should have been \$313,320 (for an application that requires clinical data for approval) rather than \$154,823 (for a supplement that requires clinical data for approval).

**IV. Assessment of Fees**

The enclosed invoice is for \$158,497, the difference between a fiscal year (FY) 2002 application fee (\$313,320) and the amount paid for the submission (\$154,823). **Payment is due within 30 days of the date of the invoice.** Instructions for payment are included in Attachment B.

If you have any questions concerning this matter or other user fee questions, please contact Michael Jones or Beverly Friedman at:

Center for Drug Evaluation and Research  
Food and Drug Administration, HFD-5

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<sup>5</sup> FDA has been sued before on dosage form determinations. In *Warner-Lambert Co. v Shalala*, 202 F.3d 326 (D.C. Cir. 2000), the Court found that FDA established criteria for dosage form classifications as "the way of identifying the drug in its physical form, which is linked both to physical appearance of the drug and the way that it is administered." In this situation, the approved product's physical appearance is one of a sponge. The physical appearance of the product submitted in the December 2001 supplement is one of a swab.

ChloraPrep S-003  
Page 5

5600 Fishers Lane  
Rockville, Maryland 20857  
301-594-2041  
FAX: 301-827-5562

e-mail: [jonesm@cder.fda.gov](mailto:jonesm@cder.fda.gov)  
[friedmanb@cder.fda.gov](mailto:friedmanb@cder.fda.gov)

We appreciate your continued cooperation and thank you in advance for your prompt payment.

Sincerely yours,



Helen S. Horn, Acting Director  
Office of Financial Management

**Enclosures**

Attachment A – Action Invoice  
Attachment B – Payment Instructions  
Attachment C – ChloraPrep Web Page

Chloraprep S-003

Page 6

HFD-5, Mediflex user fee file  
HFD-5, M.Jones  
HFM-110, C.Vincent  
HFA-120 D.Simms  
HFA-102, S.Farran  
HF-20, F.Claunts  
HFD-560, D.Hilfilker

Drafted, 4/9/2002, M.Jones  
Redrafted 5/17/2002, M.Jones  
Revised 6/18/2002, M.Jones  
Comments 6/19/2002 B.Friedman  
Edited 6/21/2002 S.O'Malley  
Revised 6/28/2002 M.Jones  
Reviewed 7/31/2002 J.Axelrad  
Revised and Final 8/8/2002 M.Jones

151  
8/8/2002

c:\data\firmcorr\letters\chloraprepv4.doc



**FDA**

**FOOD AND DRUG ADMINISTRATION  
INVOICE**

Bill Number: 1000437

Bill Date: August 16, 2002 --

**Make remittance payable to and mail to:**

**FOOD AND DRUG ADMINISTRATION  
P.O. BOX 360909  
Pittsburgh, PA 15251-6909**

**Payments sent by private courier must be addressed to:**

**FOOD AND DRUG ADMINISTRATION (360909)  
Mellon Client Service Center Rm 670  
500 Ross Street  
Pittsburgh, PA 15262-0001**

Firm ID: 13364

Firm: MEDI FLEX HOSPITAL PRODUCTS INC.

8717 WEST 110<sup>TH</sup> STREET STE 750  
OVERLAND PARK, KS

66210-2103

**TOAL APPLI CATION AMOUNT DUE:   \$158,497.00**

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*Payment must be received by the U.S. Food and Drug Administration within 30 days of the date of this invoice in U.S. dollars, by check, bank draft, or U.S. Postal money order payable to the order of the U.S. Food and Drug Administration. Any check or bank draft should be drawn on or payable through U.S. financial institutions located in the United States.*

*If full payment is not received within 30 days of the date of this invoice, an interest rate of 12.625% will be charged. In addition, delinquent invoices will be assessed a \$20 administrative fee for each full 30 day period that the account remains outstanding. A 6% late payment penalty fee also will be charged as stated in 45 CFR Subtitle A, Section 30.13.*

*A receipt will be issued upon request. The invoice will not be considered paid until payment has been cleared and the amount received by the U.S. Food and Drug Administration.*

*For further information concerning this invoice, contact: Beverly Friedman at (301) 594-2041.*

**\* See ATTACHMENT B for payment instructions . . . . .**

Firm ID: 13364  
Firm Name: MEDI FLEX HOSP PRODUCTS INC

NDA/STN	Type	CBER Userfee ID #	Clinical	Action	Action Date	Amount Paid	FY 02 Fee
N020832	SR1003		Y	Accepted for Filing	12-DEC-2001	\$ 154,823	\$ 313,320
				Total		\$	<u>158,497</u>
				Total Amount Due		\$	<u>158,497</u>

**PAYMENT PROCEDURES UNDER THE  
USER FEE PROVISIONS  
OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT**

Payment must be made within 30 days of the date of the invoice, in United States currency, by check, bank draft, or U.S. postal money order payable to the U.S. Food and Drug Administration (FDA). Please include the invoice number on your payment. Please submit the summary portion of your invoice with your payment for the full amount specified on the invoice.

Payment can be forwarded to FDA by one of the following methods:

- **U.S. Mail**  
Food and Drug Administration  
P.O. Box 360909  
Pittsburgh, PA 15251-6909
  
- **Courier Delivery:** Payments delivered by a courier service that requires a street address should be forwarded to the following address (NOTE: This address is for courier delivery only. Make sure the FDA Post Office Box Number (P.O. Box 360909) is on the enclosed check.):  
Food and Drug Administration (360909)  
Mellon Client Service Center — Room 670  
500 Ross Street  
Pittsburgh, PA 15262-0001

If a phone number is also required for the courier delivery, note 412-234-5805 on the form.

- **Wire Transfer:** Payment may also be made by wire transfer of funds. The following account identifying information is provided for firms who prefer to wire user fee payments:

**FDA Demand Deposit Account Number: 911-6309**  
**Mellon Bank Pittsburgh ABA Number: 043000261**  
**Reference: Cite the invoice number**

If full payment is not received within 30 days of the date of this letter, interest charges at the rate of 12.625% per annum will be assessed on the outstanding balance. (This rate is adjusted quarterly by the Treasury Department.) In addition, delinquent invoices will be assessed a \$20 administrative fee for each 30-day period that the invoice remains outstanding. A 6% late payment penalty will be assessed as stated in 45 CFR 30.13. Delinquent debts will be reported to credit reporting agencies and referred to debt collection agencies.

Continued on Back Page

**Attachment B – Payment Procedures (cont.)**

For firms that are delinquent in payment of fees, the Federal Food, Drug, and Cosmetic Act (the Act) states that human drug applications or supplements submitted by a person subject to fees will be considered incomplete and will not be accepted for filing by the Agency until all fees owed have been paid (21 U.S.C. 379h(e)).

It is incumbent on the firm to assure that the data are accurate and that the appropriate fees are assessed for all user fee liable applications and supplements. In addition, under section 736(i) of the Act, to qualify for a refund of any fee collected under the user fee provisions of the Act, you must submit a written request for a refund within 180 days after such fee is due. If you need more information about the applications or supplements on your invoice, waivers, reductions, or refunds, please contact Michael Jones, Beverly Friedman, or Tawni Schwemer at:

Center for Drug Evaluation and Research  
Food and Drug Administration, HFD-5  
5600 Fishers Lane  
Rockville, MD 20857  
301-594-2041  
FAX: 301-827-5562

Internet Addresses: [FriedmanB@CDER.FDA.GOV](mailto:FriedmanB@CDER.FDA.GOV)  
[JonesM@CDER.FDA.GOV](mailto:JonesM@CDER.FDA.GOV)  
[SchwemerT@CDER.FDA.GOV](mailto:SchwemerT@CDER.FDA.GOV)

Your inquiry should provide the following:

1. Company name and invoicing address
2. Invoice number (located in the upper right hand corner of the invoice)
3. Detailed description of the error or additional information requested.



[Technical Data](#) | [Applicator](#) | [News&Media](#) | [FAQs](#) | [Order Info](#) | [Contact](#) | [Medi-Flex Home](#)

 **Corporate Offices** • 8711 W. 110th Street, Suite 750 Overland Park, KS 66210-2129 • (800) 523-0502  
**Medi-FLEX Manufacturing/Distribution Facilities** • 19 Butterfield Trail El Paso, TX 79906-5248 • (800) 741-0473

## MEMORANDUM OF TELECON

DATE: January 16, 2002

APPLICATION NUMBER: NDA 21-555, Chloraprep Sepp (2% chlorhexidine gluconate) swab

**BETWEEN:**

Name: Diane Beatty, Senior Director, Pharmaceutical Development  
Phone: (913) 451-0880  
Representing: Beckloff Associates, Inc.

**AND**

Name: Babette Merritt, Project Manager  
Phone: (301) 827-2301  
Division of Over-the-Counter Drug Products, HFD-560

SUBJECT: Submission guidance

Babette Merritt informed Diane Beatty of Beckloff Associates that their December 10, 2001, submission, submitted as an efficacy supplement, was for a new dosage form and constituted a new drug application (NDA). Ms. Merritt then informed Ms. Beatty that this NDA was subject to the user fee and format requirements for NDA's.

The conversation ended cordially.

DS

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David Hilfiker  
Supervisory Project Manager

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/s/  
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Tia Frazier  
9/11/02 08:28:07 AM  
CSO

David Hilfiker  
9/11/02 04:59:23 PM  
CSO

## MEMORANDUM OF TELECON

DATE: February 26, 2002

APPLICATION NUMBER: NDA 21-555, Chloraprep Sepp (2% chlorhexidine gluconate) Swab

**BETWEEN:**

Name: Diane Beatty, Senior Director, Pharmaceutical Development  
Kathy Oliva-Whalen, Vice President, Pharmaceutical Development  
Marvin J. Sack, Associate Director, Pharmaceutics  
Phone: (913) 451-0880  
Representing: Mediflex Hospital Products, Inc.

**AND**

Name: David Hifiker, Supervisory Project Manager  
Babette Merritt, Project Manager  
Division of Over-the-Counter Drug Products, HFD-560

SUBJECT: Regulatory Guidance

**Summary:**

FDA informed the sponsor that their December 10, 2001, submission, received on December 12, 2001, would be reviewed as a new drug application (NDA), rather than as an efficacy supplement.

The Division of Over-the-Counter Drug Products agreed to request that Mr. Michael Jones, of the Regulatory Policy staff, telephone Mr. Michael Beckloff to discuss the dosage form determination as provided by FDA in today's meeting.

**Background:**

FDA provided industry attendees with a short summary of the actions that were completed to ensure this submission's correct classification as an NDA.

Industry representatives countered that the Sepp® device contained the approved 2% chlorhexidine gluconate solution, topped with a sponge and a polyester covering. As such, they did not understand why this was not determined to be a sponge as the previous Chloraprep products were.

FDA deferred to the determination provided by the Nomenclature Committee and the Office of Regulatory Policy, and informed the sponsor that this decision could be appealed.

/s/

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David Hifiker  
Supervisory Project Manager

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Tia Frazier  
9/11/02 08:17:39 AM  
CSO

David Hilfiker  
9/11/02 04:55:55 PM  
CSO

Division of OTC Drug Products Labeling Review

NDA 21-555

Submission Date: December 10, 2001

Review Date: September 18, 2002

Applicant's Representative

Michael Beckloff  
President and Chief Executive Officer  
Beckloff Associates, Inc  
Agent for Medi-Flex Hospital Products, Inc.  
Commerce Plaza II, Suite 720  
7400 West 100th Street  
Overland Park, Kansas 66210  
913-451-3955

Drug:

ChloroPrep® One-Step Sepp® (chlorhexidine gluconate 2% w/v and isopropyl alcohol 70% w/v)

Pharmacologic Category:

antiseptic

Submitted:

Carton labels for 0.67 mL Sepp Applicators 100-count package and for an individual applicator

Background:

Applicant's NDA 21-555, formerly NDA 20-832 for chlorhexidine gluconate 2% and isopropyl alcohol 70% in 3 mL applicators was approved by letter dated July 14, 2000 for the preparation of the patient's skin prior to surgery. Applicant's current efficacy supplement is for use of an additional applicator and a new indication as a patient preinjection skin preparation. The product is a 0.67 mL ampule of the same formulation in a Sepp® applicator which is the subject of a 510(k). Directions have been revised to reflect the new applicator.

Reviewer comment:

Reviewer recommended additions are identified by "redlining" (shaded text) and deletions are identified by "strikeout."

2 pages redacted from this section of  
the approval package consisted of draft labeling

Recommendations:

1. Inform the sponsor to make changes in Drug Facts labeling as follows:

Back Panel

- a. Bold the print in the warning "Flammable."
  - b. Bold the print in the warning "For external use."
  - c. Vertically align bulleted statements under "Do not use" subheading
  - d. Remove from Directions  2  
" ]" revise it to "The maximum treatment area for one applicator is approximately 2.5 by 2.5 inches," and move it to the Use section immediately after the word "injection." Health care personnel will likely see the maximum area treatable with one applicator sooner under the Use section than under the Directions section.
  - e. Debold "Call" and "(8 a.m.-5 p.m. CST)" under the section headed "Questions?"
2. Recommend to the sponsor that the Applicator label include the directions "Pinch the barrel of the applicator to break the ampule and release the antiseptic. Do not touch the applicator tip. Press the applicator tip against treatment area until liquid is visible on the skin."
  3. Request that the sponsor resubmit draft revised labels for our review and comment.

/S/

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Michael T. Benson, R.Ph., J.D.  
Regulatory Review Pharmacist

/S/

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Concurrence, Debbie Lumpkins  
Microbiologist, Team 3 Leader

cc: NDA 21-555  
HFD-560: Div. Files/Ganley/Lumpkins/Chang/Frazier/Benson

**APPEARS THIS WAY  
ON ORIGINAL**

**APPEARS THIS WAY  
ON ORIGINAL**

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/s/

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Michael Benson  
9/24/02 03:58:49 PM  
INTERDISCIPLINARY

Marina Chang  
9/24/02 04:44:12 PM  
INTERDISCIPLINARY  
for Debbie Lumpkins



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation V

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** September 26, 2002

<b>To:</b> Diane Beatty	<b>From:</b> Tia Frazier
<b>Company:</b> Beckloff Associates, Inc.	Division of Division of Over-the-Counter Drug Products
<b>Fax number:</b> (913) 451-8509 (913) 451-3846 alternate	<b>Fax number:</b> (301) 827-2315
<b>Phone number:</b> (913) 451-3846	<b>Phone number:</b> 301-827-2271
<b>Subject:</b> Discipline Review Completed for NDA 21-555 Labeling Section	

**Total no. of pages including cover:** 3

**Comments:**

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

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**Document to be mailed:**                       YES                       NO

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**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.**

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-2222. Thank you.

Before these carton and individual lid applicator labels can be approved, you must make changes in Drug Facts labeling as outlined, below.

In terms of timing of your response to this information request, we remind you that we intend to review and act on this new drug application, with or without an amendment, on or before October 12, 2002. We may defer the review of any amendments to the application that are received too close to the October 12 action deadline.

A. Carton Label

"Drug Facts" Back Panel

1. Under *Warnings*,

(a) bold "Flammable" and "For external use."

(b) vertically align bulleted statements under *Do not use*.

2. In *Directions*, revise the statement <sup>1</sup> to read "The maximum treatment area for one applicator is

approximately 2.5 by 2.5 inches." Additionally, move the same statement to the *Use* section immediately after the word "injection". Health care personnel are more likely see the maximum area treatable with one applicator sooner under *Use*, rather than under *Directions*.

3. Under *Questions*, debold "Call" and "(8 a.m.-5 p.m. CST)"

Additionally, we make the following recommendations to enhance your labeling:

4. Include the directions "Pinch the barrel of the applicator to break the ampule and release the antiseptic. Do not touch the applicator tip. Press the applicator tip against treatment area until liquid is visible on the skin" on your applicator label.

5. Resubmit draft revised labels for our review and comment.

2 pages redacted from this section of  
the approval package consisted of draft labeling

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/s/

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Marina Chang  
9/26/02 08:33:57 AM

No meetings.

## PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA #: 21-555 Supplement Type (e.g. SE5): \_\_\_\_\_ Supplement Number: \_\_\_\_\_

Stamp Date: December 10, 2001 Action Date: \_\_\_\_\_

HFD-520/560 Trade and generic names/dosage form: ChlorPrep One-Step Sepp Applicator (chlorhexidine gluconate 2% w/w and isopropyl alcohol 70% w/v).

Applicant: Medi-Flex Hospital Products, Inc. Therapeutic Class: 3S

Indication(s) previously approved: Patient preoperative skin preparation (NDA 20-832)

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 2

Indication #1: Patient preoperative skin preparation

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply:  Partial Waiver  Deferred  Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Indication #2: Patient preinjection skin preparation

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply:  Partial Waiver  Deferred  Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

### Section A: Fully Waived Studies

For Indication #1:

Reason(s) for full waiver:

Products in this class for this indication have been studied/labeled for pediatric population

Disease/condition does not exist in children

Too few children with disease to study

There are safety concerns

Other: \_\_\_\_\_

Note: This product is labeled for children 2 months of age and older (refer to review of original NDA 20-832). It is felt that the product is too irritating to test in children younger than 2 months.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

**Section B: Partially Waived Studies**

Age/weight range being partially waived:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

**Section C: Deferred Studies**

Age/weight range being deferred:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): \_\_\_\_\_

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

**Section D: Completed Studies**

Age/weight range of completed studies:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Comments:

NDA 21-555

Page 3

*If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**This page was completed by:**

*{See appended electronic signature page}*

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**David C. Bostwick, Clinical Reviewer**

**cc: NDA**

**HFD-950/ Terrie Crescenzi**

**HFD-960/Grace Carmouze**

**(revised 9-24-02)**

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960  
301-594-7337**

**Attachment A**

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: Patient Preinjection skin preparation

Is there a full waiver for this indication (check one)?

**Yes: Please proceed to Section A.**

**No: Please check all that apply: Partial Waiver Deferred Completed**

**NOTE: More than one may apply  
Please proceed to Section B, Section C, and/or Section D and complete as necessary.**

**Section A: Fully Waived Studies**

Reason(s) for full waiver:

**Products in this class for this indication have been studied/labeled for pediatric population**

**Disease/condition does not exist in children**

**Too few children with disease to study**

**There are safety concerns**

**Other: \_\_\_\_\_**

Note: This indication is included in the larger patient preoperative skin preparation indication described above.

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section B: Partially Waived Studies**

Age/weight range being partially waived:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for partial waiver:

**Products in this class for this indication have been studied/labeled for pediatric population**

**Disease/condition does not exist in children**

**Too few children with disease to study**

**There are safety concerns**

**Adult studies ready for approval**

**Formulation needed**

**Other: \_\_\_\_\_**

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section C: Deferred Studies**

Age/weight range being deferred:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): \_\_\_\_\_

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section D: Completed Studies**

Age/weight range of completed studies:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Comments:

*If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.*

This page was completed by:

*{See appended electronic signature page}*

\_\_\_\_\_  
David Bostwick, Clinical Reviewer

cc: NDA  
HFD-960/ Terrie Crescenzi  
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960  
301-594-7337

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/s/

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David Bostwick  
10/17/02 09:18:18 AM

**Review of Request for Waiver of Pediatric Studies  
NDA 21-555**

Date of Submission:      October 2, 2002

Date Assigned to Reviewer:      October 2, 2002

Date of Review Initiation:      October 3, 2002

Drug: Chloraprep® (chlorhexidine gluconate 2% w/w and isopropyl alcohol 70% w/v) One-Step® Patient Preoperative Skin Preparation

Applicant: Medi-Flex Hospital Products, Inc.  
Overland Park, KS 66210

Background: This application provides for addition of a new packaging configuration for the product, identified as a Sepp applicator; and the addition of a new indication, for patient preinjection skin preparation (for the Sepp applicator only). The revisions were first submitted as an efficacy supplement (NDA 20-832/S-003) to the original NDA, but an administrative decision was made to declare them a new NDA. Please see the Clinical Review of this material dated January 22, 2002.

Under the requirements of the Pediatric Rule, the sponsor is required to either submit pediatric studies concerning the indication addressed in the efficacy supplement, or submit a request for a waiver of such studies. The attached Pediatric Page provides an evaluation of the need for pediatric studies to support this application

/S/

\_\_\_\_\_  
David C. Bostwick, Clinical Reviewer

\_\_\_\_\_  
Jean Mulinde, M.D., Clinical Team Leader

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/s/

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David Bostwick  
10/8/02 12:17:06 PM  
MEDICAL OFFICER

Jean Mulinde  
10/9/02 01:01:39 PM  
MEDICAL OFFICER

Pediatric page entered into DFS separately

Janice Soreth  
10/17/02 04:23:18 PM  
MEDICAL OFFICER