# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION: NDA 20-774

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| Final Printed Labeling | | | X | |
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| Chemistry Review(s) | X | | | |
| EA/FONSI | | | X | |
| Pharmacology Review(s) | X | | | |
| Statistical Review(s) | X | | | |
| Microbiology Review(s) | X | | | |
| Clinical Pharmacology Biopharmaceutics Review(s) | X | | | |
| Bioequivalence Review(s) | | | X | |
| Administrative Document(s) | X | | | |
| Correspondence | X | | | |

# CENTER FOR DRUG EVALUATION AND RESEARCH

**Approval Package for:**

**Application Number: NDA 20-774**

**Trade Name: PERIOCHIP 2.5 mg**

**Generic Name:(chlorhexidine gluconate)**

**Sponsor: Target Research Associates, Inc.**

**Approval Date: May 15, 1998**

**Indication: Provides for use of the drug product as an adjunct to scaling and root planing procedures for reduction of pocket depth in patients with adult periodonititis.**

# CENTER FOR DRUG EVALUATION AND RESEARCH

**Application Number: NDA 20-774**

## APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

NDA 20-774

Food and Drug Administration
Rockville MD 20857

Target Research Associates, Inc.
Attention: Robert J. McCormack, Ph.D.
1801 East Second Street
Scotch Plains, NJ 07076

MAY 15 1998

Dear Dr. McCormack:

Please refer to your new drug application dated December 20, 1996, received December 20, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PerioChip (chlorhexidine gluconate) 2.5 mg.

We also refer you to your approvable letter dated November 25, 1997.

We acknowledge receipt of your resubmission dated December 5, 1997, received December 17, 1997. The User Fee goal date for this application is June 17, 1998.

We also acknowledge receipt of your submissions dated April 29, August 19, November 18, December 5, 9, and 10, 1997; January 13 (2), 21, March 12, and April 17 and 28, 1998.

This new drug application provides for use of the drug product as an adjunct to scaling and root planing procedures for reduction of pocket depth in patients with adult periodontitis.

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed approved labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed approved labeling text. Marketing the product with FPL that is not identical to this approved labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-774. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Roy Blay, Project Manager, at (301) 827-2020.

Sincerely yours,

/S/

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

ENCLOSURE

cc:

Original NDA 20-774
HFD-540/Div. files
HFD-540/PM/Blay (with labeling)
HFD-540/SUPV PM/Kozma-Fornaro (with labeling) 4.29.98
HFD-540/MO TM LDR/Kelsey (with labeling) 4/30/98
HFD-540/MO/Hyman (with labeling) 4/30/98
HFD-540/PHARM TM LDR/Jacobs (with labeling) 4/24/98
HFD-540/PHARM/See (with labeling) 4/29/98
HFD-540/CHEM TM LDR/DeCamp (with labeling) 5/7/98
HFD-540/CHEM/Vidra (with labeling) 5/1/98
HFD-160/MICRO TM LDR/Cooney (with labeling)
HFD-160/MICRO/Hussong (with labeling)
HFD-520/MICRO TM LDR/Sheldon (with labeling) 4/30/98
HFD-520/MICRO/Marsik (with labeling) 4/30/98
HFD-880/PK TM LDR/Bashaw (with labeling)
HFD-725/STAT TM LDR/Srinivasan (with labeling) RS 09/30/'98
HFD-725/STAT/Dixon (with labeling) CAD 4/29/98
HFD-002/ORM (with labeling)
HFD-105/Office Director (with labeling)
HFD-101/L.Carter (with labeling)
HFD-830/ONDC Division Director (with labeling)
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-95/DDM-DIAB (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-735/DPE (with labeling)
HFI-20/Press Office (with labeling)

Drafted by: rab/April 29, 1998/\c:\royblay\nda\letters\approval\20774.003
Initialed by:
final:

**APPROVAL (AP)**

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: NDA 20-774

## APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

NDA 20-774

Food and Drug Administration
Rockville MD 20857

Attention: Robert J. McCormack, Ph.D.
Target Research Associates, Inc.
1801 East Second Street
Scotch Plains, NJ 07076

NOV 25 1997

Dear Dr. McCormack:

Please refer to your new drug application dated December 20, 1996, received December 20, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Perio Chip (chlorhexidine gluconate) 2.5 mg.

We acknowledge receipt of your correspondence dated January 29 (2), February 5 and 13, May 8, June 16 (2), July 24, 29, and 30, September 5, 11, 18, 25 and 26, and October 2, 3 (2), and 14, 1997. The User Fee goal date for this application is December 20, 1997.

We have completed the review of this application as submitted with draft labeling, and it is approvable. Before this application may be approved, however, it will be necessary for you to respond to the following issues:

**Chemistry, Manufacturing, and Controls (CMC) Issues**

1. In the Regulatory Specifications & Methods Section, Vol. 1.3, p. 308, the analytical procedure is considered inaccurate and deficient. These inaccurate results lead to questionable assay results, i.e., by as much as a difference. An alternate analytical procedure is recommended, since is a known and accurate assays are essential.

2. DMF DMF, is deficient. A deficiency letter has been sent to requesting additional information on multiple issues.

The following issues are not approvability issues; however, they should also be addressed:

**Chemistry, Manufacturing, and Controls (CMC) Issues**

1. The current *in vitro* release rate specification provides only for the release rate over the first 15 hours. However, the labeling insert indicates a biphasic release in the first 24 hours followed by an almost linear release rate for 7-10 days (Vol.1.4, p. 253). Please submit release specifications for the entire 7-10 day period.

2. The aforementioned release rate assay, when conducted in an agar plate, showed a "plateauing effect" after 10-15 hours in which approximately 50-55% of the drug was released. The plateauing effect and the lack of 100% release with this assay may suggest that the highly substantive/reactive chlorhexidine gluconate reacts with and saturates the agar in the immediate location of the disk to prevent further drug release. An type of release rate assay such as the release rate assay in the biopharmaceutics section of your NDA may be more appropriate.

3. Although resins are generally tested in accordance with USP protocol and meet USP Class VI Certification, there is no specific indication that the was one of the approved resins. Please submit this information.

4. Please confirm that the sampling plan, described in the regulatory specifications section, is conducted on a "per shift" or "per batch" basis.

5. Please identify the peaks in Figure 1, Vol. 1.3, p. 274, depicting the separated

6. The molecular formula as submitted is incorrect. The correct formula (per USAN) is "$C_{22}H_{30}Cl_2N_{10}.2C_6H_{12}O_7$".

7. The investigational drug product formulations lacked specific chlorhexidine gluconate (CHG) lot numbers used in the phase 3 clinical trials. Please describe the relationship between CHG batch numbers and PerioChip lot numbers, and submit this information.

**Biopharmaceutics Issues**

1. In future submissions, when referring to concentrations of detectable substrates in the plasma and/or urine, please express such concentrations in terms of ng/ml or $\mu$g/ml as appropriate.

2. Please note that the agar plate method is inadequate as a quality control test as it does not follow the release of drug out far enough in time nor does this system mimic the mechanism of drug release *in vivo*.

3. Please note that should you wish to modify the labeling to allow for the use of more than 8 Perio Chips per subject, it may be necessary to submit new in vivo pharmacokinetic trials depending on the total number of chips used per subject.

**Microbiology Issues**

The following comments are in reference to Analytical Method which described media used for the microbial limits tests.

In addition, it will be necessary for you to submit final printed labeling (FPL) identical in content to the enclosed draft labeling. Please submit 20 copies of the final printed labeling, ten of which are individually mounted on heavy-weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below:

1. Retabulate all safety data including results of trials at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted vs now will certainly facilitate review.

2. Retabulate drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Provide details of any significant changes or findings, if any.

4. Summarize worldwide experience on the safety of this drug.

5. Submit case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

Please also update the new drug application with respect to reports of relevant safety information, including all deaths and any adverse events that led to discontinuation of the drug and any information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events. The update should cover all studies and uses of the drug including:

(1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications,
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with the Division to discuss what further steps need to be taken before the application may be approved.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, please contact Roy Blay, Ph.D., Project Manager, at (301) 827-2020.

Sincerely yours,

/S/

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure: Draft Labeling

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: NDA 20-774

## MEDICAL REVIEW(S)

NOV 1 2 1997

# Dental Officer's Review of NDA 20-774

Original NDA

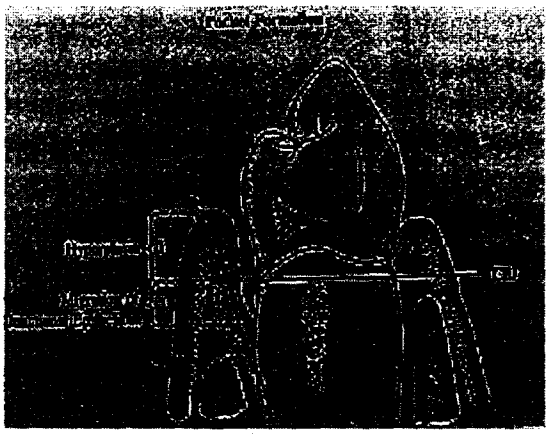
| | | | |
|---|---|---|---|
| **Drug:** | PerioChip ™ (2.5 mg. chlorhexidine gluconate bound in a hydrolyzed gelatin matrix) | **Serial Number:** | S-000 |
| | | **Submission date:** | December 20, 1996 |
| | | **Received date:** | December 26, 1996 |
| **Sponsor:** | Perio Products, Ltd. | **Review date:** | February 5, 1997 |
| | | **PDUFA date:** | **December 20, 1997** |
| **Pharmacologic Category:** | Anti-microbial | **Project Manager:** | Hal Blatt |
| **Proposed indication:** | Adjunct to scaling and root planing procedures for the treatment of periodontitis. | **Reviewer:** | Fred Hyman |

**Introduction:**

Periodontal disease is a pathogenic cascade which occurs at the supporting structures of the teeth and which, if untreated, results in the loss of connective tissue attachment, alveolar bone, and ultimately the teeth. Periodontal disease is a multifactorial process, the etiology of which may include the presence of dental plaque, microorganisms, occlusal trauma, nutritional deficiencies, and endocrinologic and hematologic influences. Some success in treating the disease or in slowing its progress has been achieved through several therapies, including surgical removal of diseased tissue, reduction of pathogens in the mouth, and reduction of the inflammatory response associated with periodontal destruction.

Gingivitis and periodontitis are the two most common periodontal diseases. Gingivitis is the general term applied to inflammation of the gingiva, which is usually the result of injury by microorganisms and their by-products, and may be either acute or chronic. The first line of defense against injury of the gingiva is the epithelium of the gingival sulcus. Once this is broken, only the resistance of the individual or the removal of the etiologic agent(s) can prevent a continuing sequence of events that may lead to advanced periodontal disease. As the inflammatory process involves the alveolar crest, the disease is called periodontitis. The periodontal fibers immediately apical to the sulcus are disrupted, and the junctional epithelium migrates along the root surface, resulting in a deeper sulcus.

A pocket is a gingival sulcus pathologically deepened by periodontal disease. It is bordered by the tooth on one side, by ulcerated epithelium on the other, and has the junctional epithelium at its base (Refer to diagram on next page). Deepening of the sulcus can occur in three ways (1) By movement of the free gingival margin coronally, as observed in gingivitis; (2) by movement of the junctional epithelium apically, with separation of the coronal portion from the tooth; and (3) by a combination of (1) and (2).



Periodontitis usually develops as a sequel to persistent chronic gingivitis and has an identical etiology. Inflammation and bacterial products spread from the gingiva to the alveolar process along the neurovascular bundle of the interdental canal at the crest of the septum. Inflammation spreads along the course of the vascular channels because the loose connective tissue surrounding the neurovascular bundles offers less resistance than the dense fibers of the periodontal ligament. Extension of the chronic inflammatory process into the alveolar bone is marked by infiltration of the marrow by leukocytes, new blood vessels, and proliferating fibroblasts. There is marked osteoclastic activity.

The current treatment for mild periodontal disease (as characterized by inflamed gingiva with pocket depths of approximately 4 mm.) consists of scaling and root debridement combined with plaque control. As the pocket deepens, however, scaling and root planing may become less effective and a significant amount of bacteria may remain, exacerbating the tissue destruction that accompanies periodontal disease. The limitations of scaling and root planing in reaching the pocket base have resulted in the use by clinicians of adjunctive antibiotics. Use of an agent that helps reduce bacteria in the base of the pocket may be helpful in preventing the progression of periodontitis by reducing the inflammation that accompanies bacterial presence. This reduction in inflammation may also help to break the cycle of further bacterial accumulation by maintaining or reducing the depth of the gingival pocket (which traps the bacteria), thereby making the pocket more accessible for cleansing.

Chlorhexidine in the form of 0.12 % chlorhexidine gluconate (CHG) oral rinse was approved on August 13, 1986 as NDA 19-028. Its current indication is for "*use between dental visits as part of a professional program for the treatment of gingivitis as characterized by redness and swelling of the gingiva including gingival bleeding upon probing.*" Procter and Gamble has marketed this drug as Peridex® since its approval, and Colgate-Palmolive recently introduced a generic form as well. Clinically, mouth rinsing trials ranging from 3 weeks to 2 years have shown that 0.12 % chlorhexidine delivered as a mouthrinse exerts a significant bacteriostatic effect which, compared with placebo or other active controls, can significantly reduce plaque and gingivitis occurrence; best results occur when chlorhexidine is used in combination with tooth brushing and flossing. No clinical advantages of higher concentrations of CHG over the 0.12% mouthrinse in reducing plaque or gingivitis were noted; however, twice daily rinsing appeared to be a more clinically effective regimen than once daily. Significant reductions of microbes on teeth support the clinical findings of decreased plaque and gingivitis. There were, however, no notable or significant differences in changes of pocket depth or attachment level, suggesting that chlorhexidine used in mouth rinse formulations, while controlling plaque and

gingivitis, does not penetrate the periodontal pocket, and therefore may not be clinically advantageous in preventing more severe periodontal disease. Irrigating the gingival pockets with a chlorhexidine rinse prior to scaling and root planing demonstrates some improvement in the amount of plaque and gingivitis present; however, sub-gingival irrigation into pockets after scaling and root planing has been shown to be of little or no benefit. The chlorhexidine provided by local irrigation to the gingival pockets is not maintained for a sufficiently sustained time in the crevicular fluid.

Systemic antibiotic administration has the advantage of treating the entire oral cavity; however, high doses must be administered, potential drug toxicities may occur, there is potential for antibiotic resistance to develop, and patient compliance is often poor. These drawbacks to systemic administration of antibiotics have led to the testing of local delivery systems, in which antibiotics such as tetracycline, metronidazole and chlorhexidine are delivered directly to the site of gingival inflammation. Tetracycline has been successfully used in this fashion as an adjunct to scaling and root planing in the form of an impregnated fiber, which was approved and is marketed as Actisite™. The sponsor of this NDA believes that chlorhexidine is the drug of choice to be delivered in a sustained release fashion into the periodontal pocket for the treatment of mild periodontal disease largely due to the issue of resistance. Although development of bacterial resistance to metronidazole and tetracycline has been known to occur, no significant increase in resistance of plaque bacteria to chlorhexidine has been shown. The development of chlorhexidine for use as a topical antibacterial in the trials that accompany this NDA was done with the purpose in mind of reducing bacteria and their inflammatory byproducts in the gingival sulcus of mild to moderately affected sites, which in turn, would help to prevent further inflammation and the advancing cycle of more severe periodontal disease.

Chlorhexidine is a strongly dibasic bis-biguanide. The chlorhexidine cation reacts with negative charges on the bacterial cell. As a result, cell surface enzymes are inactivated, and the cells surface is damaged. The permeability of the cell is so altered that chlorhexidine diffuses into and causes precipitation of the cytoplasm. It is effective in the μg/mL range against organisms implicated in gingivitis such as actinomyces and fusobacteria as well as putative periodontopathogens such as *Bacteroides* and *Prevotella*. It is also effective against candida, yeasts, some viruses, and amoebae. Chlorhexidine in saliva is antimicrobially active.

Chlorhexidine binds to protein - its two guanidine groups form a reversible, electrostatic interaction with amino acids with acidic protein side chains. Due to the reversible interaction of CHX with the proteins adsorbed to the oral cavity mucous membrane, the CHX is then released over time, resulting in a substantial but progressively decreasing concentration of salivary CHX for 8-12 hours. The protein-binding property of chlorhexidine is probably the main cause for the substantivity of chlorhexidine oral rinse to the mucous membrane of the oral cavity. Similarly, this property of protein binding plays an important role in PerioChip™, which makes use of a biodegradable cross-linked gelatin matrix to dispense chlorhexidine at

levels of up to 2000 μg/mL. The chlorhexidine in the PerioChip™ binds reversibly in an electrostatic interaction with the hydrolyzed gelatin of the cross-linked matrix. The binding of chlorhexidine to protein matrix assists both in controlling the amount of chlorhexidine released via diffusion, and in inhibiting collagenase degradation of the chip matrix. In vitro release kinetic studies demonstrated that initially about 40% of the chlorhexidine is released in a "burst" effect, probably via diffusion from the outer layers of the matrix. During this time, there is probably minimal enzymatic biodegradation of the chip since the high concentration of chlorhexidine interferes with the activity of collagenase. Twenty four hours after the initial partial depletion of chlorhexidine, matrix degradation begins, allowing further release.

**Background and Regulatory History**

*Note: Abbreviations are defined at first use. For quick reference, a glossary is included at the end of this review with full definitions of terms.*

Chlorhexidine has been marketed in the United States in professional use products such as surgical hand scrubs, health-care personnel handwashes and patient preoperative skin preparations under the NDA process. The first NDA for a chlorhexidine product was for the drug Hibiclens, which was approved in 1976. Chlorhexidine has been approved for use in a total of 12 products through the NDA process. In response to the agency's proposed rule published in 1977 for OTC topical antiseptic products, numerous requests to include chlorhexidine gluconate in the monograph were submitted. The agency responded to the requests in an amended proposal published in 1994 and stated that there were insufficient data available in the public domain to support its inclusion in the monograph. In response to the amended proposal, the agency has again received comments to include chlorhexidine in the final rule, and is again under review.

Currently, the only FDA-approved chlorhexidine-containing dental product in the United States is 0.12 % chlorhexidine gluconate oral rinse, which was approved on August 13, 1986 as NDA 19-028. Its current indication is "for use between dental visits as part of a professional program for the treatment of gingivitis as characterized by redness and swelling of the gingiva including gingival bleeding upon probing." Procter and Gamble has marketed this drug as Peridex® since its approval, and Colgate-Palmolive recently introduced a generic form as well.

Perio Products, LTD, a company based in Jerusalem, Israel, opened IND for the purposes of investigating the safety and efficacy of PerioChip™. On the IND was placed on clinical hold because the sponsor had opened the IND with a proposed Phase 2 trial without providing human safety data. The deficiencies were resolved and the sponsor was allowed to resume clinical trials This NDA was received on December 20, 1996, and accepted for filing on February 18, 1997. The User Fee Goal date is December 20, 1997.

During the meeting, discussion on pivotal protocol design was held. It was agreed that the duration of the trial would be 9 months, rather than 6. It was also agreed that a "no treatment arm" was not necessary - although the FDA stated that there were inadequate data to validate the used of scaling and root planing as a positive control, the sponsor responded as follows: 1) Scaling and Root Planing (SRP) is the currently accepted treatment method in the U.S., 2) Since PerioChip™ is an adjunct to SRP, and is not intended as a stand-alone treatment, it would not require comparison to SRP, and 3) SRP changes from baseline will "validate SRP". It was agreed that the FDA would not insist on a "No-Treatment" arm, although a statement was made that lacking this arm may affect efficacy analysis and resultant approval.

*Reviewer's comment: The current policy on the Division is to accept the following three arms for an adjunctive indication (therapy in combination with SRP) for this type of product:*

1. *Active + SRP*
2. *Vehicle + SRP*
3. *SRP alone*

*While a fourth arm that would enroll subjects who receive no treatment would be helpful to provide quantitative data on the therapeutic benefit of SRP, it is not a requirement. Since the literature is in agreement that SRP is the standard of care for treatment of periodontal diseases, a product making an adjunctive claim would need to demonstrate superiority to SRP alone but not need to reaffirm the effectiveness of SRP. Although it is generally accepted that SRP will result in approximately a 1 mm improvement in periodontal pocket depth, this figure has a lot of variability associated with it. Improvement in Probing Pocket Depth (PPD) is affected by extent of disease at baseline, training of the investigators and examiners in administering SRP and reading pocket depths, compliance of subjects with oral hygiene during the trial. The most recent guidelines of the American Dental Association for acceptance of products for professional, non-surgical treatment of adult periodontitis (Imrey PB, Chilton NW, et al. Proposed guidelines for American Dental Association acceptance of products for professional, non-surgical treatment of adult periodontitis, J Periodont Res 1994: 29: 348-360) contains a discussion on utilization of a negative control when testing a new therapy for adult periodontitis as follows:*

> *"The Task Force feels that existing pre-post data on response to SRP furnish adequate reference against which to gauge the performance of SRP in a new study. The magnitude of SRP's effect relative to negative control, while of scientific interest, is of little relevance in evaluating a new adjunctive product. The ethical justification for*

*withholding SRP from any study subjects in these circumstances is controversial, while the associated costs of an additional control group are substantial, and the benefits are largely conjectural."*

The sponsor stated that since "successful SRP provides 0.5 to 1.0 mm reduction in PPD, an additional 0.4 mm above SRP is needed for the PerioChip™ to show efficacy" (Page 385, Volume 1, NDA submission). The sponsor also stated that the PerioChip™ was not expected to improve the attachment level, but they did not expect the chip to cause a worsening of attachment. It was therefore agreed that the primary efficacy variable will be a reduction in PPD and no worsening of Probing Attachment Level (PAL) by ≥ 20%.

*Reviewer's Comment: Refer to the Discussion section of this review for comments on the relationship between PPD and PAL.*

At the meeting, the Agency primarily discussed acceptability of the NDA for filing. However, the sponsor notes in the NDA submission that during this meeting, the issue of clinical significance was addressed. According to the sponsor, it was decided that a reduction in PPD of 2 mm or more should be analyzed on a per patient basis. A pocket reduction of 2 mm. is one that can easily be measured by the periodontist or general dentist and will impact on the treatment plan for the patient, often changing a treatment plan that includes advanced periodontal therapy to one that includes maintenance treatment only. The Agency's minutes, while in agreement on the filability issues, do not reflect a discussion that transpired regarding clinical significance.

*Reviewer's Comment: The analysis of data in this manner was not proposed as either a primary or secondary variable prior to the onset of the trial. The first mention of this analysis was made during the meeting. Because this analysis may have been conducted after an initial look at the data, FDA's statistician was consulted about whether the p-value would need to be adjusted due to a penalty. There was concern that several values were examined before finding the 2 mm. value that gave the best level of significance. Since p-values for the hypotheses testing in both pivotal trials were less than 0.005, even with a correction for multiple testing, each trial still maintains an overall significance at less than 0.05. See Discussion section of this review for further discussion of the significance of this analysis.*

<u>Executive Summary</u>

In this NDA submission, the sponsor has submitted data and supporting documents in an attempt to justify the claim that this chlorhexidine-impregnated gelatin chip, when used as an adjunct to regular scaling and root planing treatment, effectively reduces probing pocket depth (PPD) and bleeding on probing (BOP) while maintaining the probing attachment level (PAL) in the treatment of periodontitis. After thorough review, the claim,

was disallowed because the sponsor has not successfully demonstrated

reduction of the incidence of in both pivotal trials. Although PerioChip™ has demonstrated statistically significant reduction of pocket depth which would be useful in a periodontal maintenance program, this outcome alone is not sufficient to claim of Therefore, the allowable claim for this product is as follows: PerioChip™ is indicated as an adjunct to scaling and root planing for reduction of pocket depth in patients with adult periodontitis.

Results of three Phase 3 trials as well as earlier Phase 2 trials and pharmacokinetic studies were submitted to the NDA. In the two U.S. trials, subjects were entered into the trial who had at least four teeth with mild to moderate periodontal disease. In one group of subjects, two randomized target sites received a PerioChip™ after SRP and the other two sites were followed as the SRP-only treatment. In the other group, two randomized target sites received a placebo chip after SRP, and the other two sites were followed as the SRP-only treatment. In the one multi-center Phase 3 trial that was conducted in Israel and Europe, the protocol was somewhat different than the two US trials. PerioChip™s were placed in any eligible tooth site in a randomly selected upper quadrant. As a result the number of chips inserted in a single patient quadrant at any visit ranged from 1 to 15 with an average of 4.

Of the three Phase 3 trials submitted to this NDA for review in support of the safety and efficacy of the PerioChip™, the foreign trial, #92-002, was by the sponsor's own admission, not considered to be pivotal for several reasons. It used a split-mouth design, in which one half of the mouth was treated with active, and the other half was the control. The split mouth design, because of its propensity for spill-over effect of the active, is looked upon with reservation by the Agency. In addition, there was no placebo group in this trial, so potential unblinding and bias is a consideration. Furthermore, smokers were eliminated entirely from the European trials, rather than included and examined separately as in the other two trials. Also, the European/Israeli trial was only of 6 months duration, which, although acceptable is not as informative a the U.S. trials of 9 months duration. Finally, this trial was conducted in Europe and Israel, which would require demonstration of comparable U.S. demographics. The other two Phase 3 trials were both parallel, randomized, double-blinded, placebo-controlled trials, each conducted in five U.S. centers. Both of these U.S. trials, #94-002, and 94-003, met the Agency criteria of well-controlled clinical trials.

*Efficacy*

Following this section of the review is a table for the clinical trials that summarizes changes in PPD, PAL, and BOP. A complete discussion of the specific elements of these trials can be found in the appropriate sections of this review. In the pivotal trials, PPD and PAL were identified *a priori* as the primary efficacy variables, and BOP, Plaque Index (PI), Gingival Index (GI), and Staining Index (SI) were secondary. Out of the secondary outcome variables, BOP was the only one that the sponsor was interested in using in labeling. The PI and GI did not show sufficient improvement to make claims, and the SI was used to demonstrate a lack of

staining from the chlorhexidine, which it did. Measurement of both primary and secondary outcomes were made at Week 6, Month 3, Month 6, and Month 9. In the non-pivotal Phase 3 trial, only PPD was a primary outcome variable; PAL, BOP, PI, GI, and SI were all secondary. The non-pivotal Phase 3 trial was only of 6 months duration.

**Summary Table for Phase 3 Clinical Trials NDA 20-774**

| Trial | | 94-002 | 94-003 | 92-002 |
|---|---|---|---|---|
| Location | | Alabama, North Carolina, Missouri, Virginia, Florida | New York (Buffalo and Rochester), New Jersey (Paramus and Newark), Wisconsin | Jerusalem, Israel; Newcastle, UK; Strasbourg, France |
| Number Subjects Enrolled | | 215 | 232 | 172 |
| Probing pocket depth (PPD) | Reduction at 9 months of PerioChip™ + SRP above and beyond SRP alone (in mm.) | 0.29 | 0.32 | 0.43 |
| | Statistical Significance? | p <0.006* | p <0.001* | p <0.001* |
| | Percent of Sites at 9 months with PPD Reduction ≥2.0 mm. in PerioChip™ + SRP above and beyond SRP alone (in mm.) | 18.7% | 15.3% | 9.6% |
| | Statistical Significance? | p <0.004* | p <0.001* | p <0.017* |
| Probing attachment level (PAL) | Reduction at 9 months of PerioChip™ + SRP above and beyond SRP alone (in mm.) | 0.23 | 0.10 | 0.20 |
| | Statistical Significance? | p <0.11 | p <0.10 | p <0.003* |
| Bleeding On Probing (BOP) | Percent of sites improved at 9 months in PerioChip™ + SRP above and beyond SRP alone | 12.7% | 10.4% | 18.0% |
| | Statistical Significance? | p <0.018* | p <0.146 | p <0.004* |
| Pivotal for | Efficacy? | Y | Y | N |
| | Safety? | Y | Y | Y |
| Comments | | | | The length of this trial was only 6 months. |

For the purposes of efficacy, the two pivotal trials will be judged significant; the European Phase 3 trial, as well as results from the Phase 2 trial, will be used as supporting evidence of efficacy. The sponsor demonstrated a statically significant improvement in PPD in both pivotal trials, with a mean magnitude of improvement equal to 0.29 mm in one trial and 0.32 mm improvement in the other above and beyond that of the SRP-only groups, with both results being highly significant. Because the sponsor was not successful at achieving a difference of 0.4 mm. or greater, as they had proposed prior to conducting the trial, they examined the data in another way, which was recommended by the Task Force on Design and Analysis in a publication made in 1994, after the trials were initiated (See *Discussion* section of this review for further discussion of the significance of this analysis). The task force recommended analysis of the number of sites improved by 2.0 mm or greater in the test product compared to the control when examining soft tissue changes such as attachment level or probing depth. In this case, the sponsor was able to demonstrate that while 16.9% of the subjects in the SRP-only group had one or both treated sites improve by 2.0 mm or more, 35.6% of the PerioChip™ +SRP sites also improved by 2 mm or more ($p < 0.004$) in study 94-002. In Study 94-003, 10.2 % of the subjects in the SRP-only group had one or both treated sites improve by 2.0 mm or more, whereas 25.5% of the PerioChip™ +SRP sites improved by 2 mm or more ($p < 0.001$).

The sponsor had stated prior to initiating the trials that they did not expect PAL to achieve a significant difference in the PerioChip™ group compared to placebo or active control. Therefore, they had presented to the Agency, and it was agreed at the End-of-Phase 2 meeting, that PAL would be used as a primary outcome variable in the sense that it would not worsen as a result of the treatment. In fact, the sponsor was able to demonstrate that PAL improved above and beyond the improvement of SRP alone or SRP +Placebo chip in both trials, although not to the same extent as PPD. Statistical significance was reached only in the PAL comparison of PerioChip™ +SRP to Placebo Chip +SRP in study 94-002, with a 0.28 mm greater improvement in the PerioChip™ group ($p < 0.035$). At first appearance, it is inconsistent that the active treatment arms were able to demonstrate consistently significant improvement in PPD, but not in PAL. It follows that if the reduction in bacteria at the base of the pocket results in reduction of PPD, then PAL should improve as well. According to the sponsor, the smaller decrease in the magnitude of change observed for PAL compared to PPD (and resulting lack of statistical significance in 3 of the 4 comparisons) results from two factors: (1) greater variability in the measurement of PAL compared to PPD and (2) the additional component of PPD reduction that results from the apical positioning of the gingival margin due to tissue shrinkage. The sponsor's definition of success in the primary outcome variable for PAL as "stabilization" was probably an attempt to err on the conservative side of expected effect. Certainly, although the magnitude of change in PAL is not as great as is seen with PPD, the trend is quite strong and supportive. The sponsor's explanation is reasonable.

Bleeding on probing, although considered a secondary efficacy variable in all three Phase 3 trials, was important to the sponsor for the purposes of labeling. The results of BOP in their two pivotal trials were mixed, and therefore, equivocal. BOP was a categorical variable, with either a "yes" or "no" outcome for bleeding at each site measured. Because BOP was an inclusionary criterion for the trials, all subjects began the trial with BOP. Success was measured as a significant percent of sites that converted to non-bleeding. The sponsor performed an analysis of the results by observation period, which provided the following information: In study 94-002, the distribution of bleeding sites showed that PerioChip™ sites experienced fewer bleeding episodes compared to both control groups (SRP alone and placebo chip sites) at Week 6 ($p < .05$), Month 6 ($p < .05$) and Month 9 ($p < .05$). In study 94-003, Week 6 was the only time point in which subjects who received PerioChip™ experienced fewer bleeding episodes compared to both control groups; however, this result did not reach statistical significance. At Month 6, the PerioChip™ plus SRP group experienced significantly more bleeding episodes compared to the SRP alone group ($p = 0.062$). Clearly, these results do not support a conclusive BOP outcome with the application of PerioChip™. The recommendation of this review is to delete references to BOP reduction in the label.

Two other secondary efficacy variables, GI and PI, showed mixed results and were therefore not supportive of a trend. The overall conclusion is that there was no difference demonstrated. The sponsor has explained in the submission that significant differences were not expected in either of these outcome measures, because the PerioChip™'s activity occurs primarily under the gumline, whereas GI and PI are supragingival measurements. In addition, since all groups received a thorough dental prophylaxis at baseline, supragingival reduction in inflammation would have occurred uniformly in all groups at the outset of the trial.

Stain monitoring was selected as another secondary efficacy variable, as a result of staining being a documented adverse event resulting from chlorhexidine rinse use. Considering this an efficacy variable is probably a misnomer, as there was never a hypothesis that chlorhexidine chip placement would reduce stain - rather, it was monitored to determine whether the label should warn of staining as an adverse event. Both pivotal trials exhibited no observable stains on supragingival tooth surfaces at baseline and there was little change in the SI over the treatment period in any of the treatment groups. Due to the lack of any significant occurrence of staining, no warning is required on the label.

*Safety*

Unlike the efficacy deliberations, which weighed the two pivotal trials most heavily, all clinical trials were appraised in the consideration of safety. Safety has been demonstrated through monitoring of adverse events in each of the Phase 2 and Phase 3 trials submitted, as well as through a separate pharmacokinetics study. No reports of serious adverse events were submitted that were related to use of the product. Reports of transient dental pain immediately after SRP plus placement of the PerioChip™ were noted. The PerioChip™ group reported an

incidence of 51%, whereas the placebo chip reported 41% for this adverse event. Generally, the discomfort was mild to moderate in nature. How much of this is associated with the SRP procedure is unknown, since both groups received SRP prior to the chip placement. It should be noted that 70% of the toothaches occurred within the first 3 months of the trials, especially within the first week of the study, strongly suggesting that they were related to the SRP procedure along with chip placement. Although both the placebo and PerioChip™ subjects reported high incidences of toothache, the statistically significant difference supports the notion that the active ingredient also contributed to the discomfort. As a result of the high overall incidence of toothache, and the association with the PerioChip™, the labeling should clearly reflect this potential adverse event.

*Labeling*

*Conclusions*

The sponsor has successfully demonstrated the safety and efficacy of PerioChip™. With modifications in labeling, the product may be approved for marketing.

**Chemistry and Manufacturing Controls Summary**

This NDA has a 3-S classification for a new drug dosage form. Each 7.4 mg PerioChip contains 2.5 mg chlorhexidine gluconate. The drug substance to be used in the commercialized drug product is manufactured by while the drug substance used in pivotal clinical trials was manufactured by . **The reviewing chemist noted several deficiencies, which, until corrected, will not allow for an approval recommendation from Chemistry.** Some of these deficiencies include an inaccurate assay of p-chloroaniline (a metabolite of chlorhexidine and a known carcinogen), incomplete release rate specifications, insufficient information about testing, sampling plan concerns, and unidentified lot numbers. Refer to the Chemistry review for detailed information.

**Pharmacology/Toxicology Summary**

Chlorhexidine was not detected in plasma or urine samples obtained during clinical studies, and chlorhexidine is known to be very poorly absorbed from the GI tract. Data from a 30-day toxicity study in rats, although inconclusive, tend to support safety of the test material. PerioChip™ units did not appear to be excessively irritating in hamster cheek pouch studies, producing only minor reversible reactions. Since PerioChip™ units are not proposed for chronic use, this NDA does not require fertility studies. For the same reason, carcinogenicity assessment is unnecessary. Chlorhexidine was not maternally toxic or teratogenic in rats. Based on its history of safe use and extremely low exposure in PerioChip™, additional teratology data is not required. Mutagenicity studies do not provide evidence of genetic toxicity potential. The pharmacologist recommended approval in regard to pharmacologic and toxicologic concerns with suggested modification of the wording in both the *Pregnancy category* and *Carcinogenesis, Mutagenesis, Impairment of Fertility* sections of the label. Refer to complete Pharmacology/Toxicology review for further details.

**Pharmacokinetic Summary**

PerioChip™ units are intended to provide sustained release of chlorhexidine within a periodontal pocket, resulting in maintenance of the chlorhexidine concentration of the gingival crevicular fluid (GCF) above the minimum inhibitory concentration (MIC) for suspected pathogens. The submission states that placement of a PerioChip™ unit results in high initial levels of chlorhexidine in the GCF ($C_{max}$ of 1100 to 2000 $\mu$g/ml, $T_{max}$ 1 to 2 hours), followed by a gradual decline in the concentration, such that the concentration of chlorhexidine int he GCF is maintained above the MIC of "99% of subgingival bacteria" (125 $\mu$g/ml) for 7 to 10 days. Since the efficacy of the PerioChip™ is based on the localized release of chlorhexidine, bioavailability, for purposes of this NDA, will be defined as the release of chlorhexidine from the PerioChip™ into gingival crevicular fluid.

The mechanism of PerioChip™ degradation within the periodontal pocket and concomitant chlorhexidine release into the GCF involves two processes: diffusion and enzymatic degradation. The PerioChip™ matrix consists of hydrolyzed gelatin cross-linked with glutaraldehyde to form an insoluble compound that can only be dissolved by proteolytic enzymes. On the other hand, the high concentrations of chlorhexidine incorporated in the matrix partially inhibit the enzymatic degradation of the chip matrix. These two unique but complementary properties of the PerioChip™ regulate the rate of chlorhexidine release and matrix degradation in the periodontal pocket.

In vitro release kinetic studies demonstrated that initially about 40% of the chlorhexidine is released in a "burst" effect, probably via diffusion from the outer layers of the matrix. During this time, there is probably minimal enzymatic biodegradation of the chip since the high concentration of chlorhexidine interferes with the activity of collagenase. Twenty four hours after the initial partial depletion of chlorhexidine, matrix degradation begins, allowing for further release of chlorhexidine.

A pharmacokinetic study was conducted with 19 human subjects, each receiving 4 PerioChip™s whose GCF was sampled at 0, 2, 4, 24, 48, 72, 96, 120, 168, 192, and 216 hours after placement. Samples of blood and urine were collected 24, and 96 hours after placement, with blood sampling also being taken at 48 hours. It was demonstrated that the concentration of chlorhexidine in the GCF peaked within two hours after placement, remained fairly constant through 72 hours post-placement, and tapered over the remainder of the observation period. Chlorhexidine was not detected in any plasma sample or in any urine sample. The limit of quantitation for the analytical method that was used was 30 ppb.

Although the sponsor has requested the use of 8 PerioChip™s at any one time, in vivo pharmacokinetic information was only provided for the use of 4 PerioChip™s. As a result of this concern, additional information from the literature as to the absorption of chlorhexidine following oral administration was requested. The biopharmaceutics reviewer concluded that

the information provided by the sponsor in combination with the *in vivo* data are sufficient to support the use of up to 8 PerioChip™s at any one time in a patient.

**Microbiology Summary**

The antimicrobial spectrum of activity of chlorhexidine includes vegetative gram-positive and gram negative bacteria inclusive of vegetative anaerobes. At low concentrations chlorhexidine tends to be bacteriostatic while at higher concentrations it is bactericidal. The main site of action of chlorhexidine is the cellular membrane of bacteria, resulting in dissolution of the membrane with resulting leakage of the cytoplasmic content. Despite the use of chlorhexidine in a variety of products for over 40 years, no conclusive evidence exists in the literature that microorganisms have developed resistance to it. The sponsor has provided data which indicates that the use of chlorhexidine has a very low potential of causing a shift in the residing micro flora so as to cause colonization or overgrowth in the oral cavity of undesirable organisms. Chlorhexidine has been shown to have clinically relevant activity against those bacteria which have been associated with periodontal disease. The microbiology review supports the sponsor's contention of an association between elimination or reduction in the population of potential periodontal pathogens by PerioChip™ and reduction in probing pocket depth. Refer to the complete Microbiology review for further details.

# Clinical Trials

*The first part of this section of the review contains a summary of Phase 2 studies and a non-pivotal Phase 3 study. The second part contains a detailed discussion of the two pivotal trials, including inclusion and exclusion criteria, study plan, and results. A separate discussion section follows, in which the results of all (but focusing primarily on the two pivotal) trials, will be analyzed and evaluated in terms of how they support the sponsor's conclusions.*

## *Summary of Non-Pivotal Phase 2 and Phase 3 studies*

**Study No. 91-013**

A Phase 2 study was initiated in 1992 with 41 subjects, evenly split between men and women and ranging in age from (Mean age: 45.7). The split-mouth study was of 6 months duration and included the following four treatments - 1 active chip, 2 active chips (1 at baseline and the second after one week), 2 placebo chips and no treatment. In this trial, the subjects, whose mean pocket depth at baseline was approximately 6 mm, received only supragingival scaling and polishing at baseline.

**Reduction from Baseline for Primary Efficacy Variable - PPD**

**Study No. 91-013**

| Treatment | Baseline PPD | PPD reduction in mm from Baseline | | |
|---|---|---|---|---|
| | | Month 1 | Month 3 | Month 6 |
| Single PerioChip™ | 6.08 ± 0.16 | 0.59 ± 0.14 | 0.72 ± 0.14 | 1.00 ± 0.16 |
| Two PerioChip™ | 6.02 ± 0.11 | 0.02 ± 0.15 | 0.42 ± 0.18 | 0.63 ± 0.19 |
| Placebo Chips | 6.05 ± 0.14 | 0.02 ± 0.15 | 0.31 ± 0.16 | 0.69 ± 0.11 |
| No Treatment | 6.19 ± 0.17 | 0.19 ± 0.12 | 0.64 ± 0.16 | 0.75 ± 0.13 |

The single PerioChip™ group had a significantly greater improvement in PPD at one month compared with both the no treatment group and the placebo group. By the sixth month, the improvement as measured by the other groups' decreasing pocket depths obliterated the statistical significance between the PerioChip™ group and the other two. Nonetheless, the trend was present that the single PerioChip™ group performed better than placebo or no treatment. The sponsor hypothesized that the two-chip treatment, although providing more chlorhexidine to the periodontal pocket, may also have interrupted the healing process as a result of an additional tissue manipulation. The outcome of this study determined the dose of the PerioChip™ regimen, a single application every three months.

DNA Analysis of PerioChip™ Versus Placebo Chip

As a part of the DNA analysis of microflora in the PerioChip™ versus placebo chip groups, the following species were examined: P. gingivalis, P. intermedia, B. forsythus, W. recta, E. corredens, and A. actinomycetemcomitans. Comparing the concentrations as transformed to log CFU/mL revealed consistently lower readings in the PerioChip™ group at all time points examined for all these bacteria. Significant reductions of B. forsythus and W. recta were noted at Month 6 for the PerioChip™ compared with the placebo chip. Numerical trends favoring the PerioChip™ resulted in significantly greater reductions than placebo chip in P. gingivalis, P. intermedia, and B. forsythus at Month 1.

Safety Results

A total of 28 adverse events were reported by 22 of 41 (54%) subjects. All of the adverse events reported during the study involved the oral cavity; the most frequent AE's were dental pain and gum discomfort that were resolved without drug therapy. Refer to the Discussion section of this review for comments on integrated safety of all trials.

**Study No. 92-002**

This Phase 3 European/Israeli Study was conducted to determine the effect of placement of a PerioChip™ as an adjunct to regular treatment on probing pocket depth after scaling and root planing. Although this was a multicenter, randomized trial, its split mouth design and the lack of a placebo group prevent it from being considered as one of the pivotal trials for NDA approval. Although the sponsor considers this a blinded trial, since the subjects know which side of their mouth received the PerioChip™s, even maintenance of a single-blind is questionable.

In this trial, all eligible subjects with baseline pockets between 5 and 8 mm. were given a subgingival and supragingival scaling and root planing administered to all teeth. PerioChip™s were inserted in all the qualifying target sites within a quadrant; the other quadrant received no further treatment. The protocol design allowed for insertion of PerioChip™s in any eligible tooth site in a randomly selected upper quadrant. As a result, the number of chips inserted in a single patient quadrant, at any visit, ranged from 1 to 15, with an average of 4. At Month 3, all previously treated pockets in the PerioChip™ quadrant with a probing pocket depth of 5 mm or more received another PerioChip™ and a full-mouth supragingival scaling was performed.

*Reviewer's Comment: Unlike the protocol for this trial, the protocols that were followed during the pivotal trials called for all pockets with a probing pocket depth of 5 mm or more to receive another PerioChip™ or placebo chip (depending upon group assignment) without scaling. A routine "periodontal prophylaxis" was scheduled for the last visit of the pivotal trial, at 9 months. (See discussion of Pivotal Trials, in a later section of this review.)*

**Reduction from Baseline for Primary Efficacy Variable - PPD**
***92-002***

| Treatment | Mean Baseline PPD(mm ± SD) (N = 155) | Mean PPD Reduction from Baseline (mm ± SE) | | |
|---|---|---|---|---|
| | | Month 1 (N = 155) | Month 3 (N = 145) | Month 6 (N = 135) |
| PerioChip™ + SRP | 5.94 ±0.76 | 0.54 ±0.04 | 0.92 ± 0.04 | 1.32 ±0.05 |
| SRP alone | 5.85 ±0.71 | 0.54 ±0.04 | 0.65 ±0.04 | 0.89 ±0.04 |
| Difference<br>p-value | | 0.000<br>0.989 | 0.27<br><0.001 | 0.43<br><0.001 |

Safety Results

All subjects in this trial were assessed for safety. During the study, 148 adverse events were reported for 95 (55%) of the subjects enrolled. A total of 85 of these events experience by 57 subjects were considered to be related to the scaling and root planing procedure and/or the PerioChip™ insertion. The most common treatment-related adverse events were toothache, tooth disorder, and gingival pain. Refer to the Discussion section of this review for comments on integrated safety of all trials.

## Pivotal US Studies: 94-002 and 94-003

These two Phase 3 trials are submitted as pivotal. Because they used identical protocols, they will be reviewed together. Results will be identified by trial number. The Discussion Section of this review will address the conclusions from each of the trials.

| | |
|---|---|
| **Phase:** | 3 |
| **Title:** | Clinical Effects Following Subgingival Administration of Chlorhexidine Gluconate (2.5 Mg) in a Cross-Linked Gelatin Matrix in Patients With Chronic Periodontitis |
| **Objective** | To determine the effect of placement of a PerioChip™ with chlorhexidine as an adjunct to regular scaling and root planing treatment on the reduction of probing pocket depth (PPD) and on the maintenance of probing attachment level (PAL). |
| **Principal Investigators and Associated Study Site:** | 94-002:<br>Jeffcoat, University of Alabama, Birmingham<br>Offenbacher, University of North Carolina<br>Killoy, University of Missouri, Kansas City<br>Magnusson, University of Florida<br>Gunsolley, Virginia Commonwealth University<br><br>94-003:<br>Ciancio, State University of New York at Buffalo<br>Fine, University of Medicine and Dentistry of New Jersey<br>Lowenguth, Eastman Dental Center<br>Gordon, TKL Research, New Jersey<br>Dentino, Marquette University |

**Number of Subjects:** 215 - 102 Males, 113 Females (94-002)
232 - 105 Males, 127 Females (94-003)

**Ages of Subjects:** 27 - 78 Mean age 47
31 - 79 Mean age 47

**Inclusion Criteria:**

1. Adult patients (aged 30 - 80)
2. Good general health
3 At least four teeth with probing depth of 5 - 8 mm
4. Target teeth with the following:
   a. Must demonstrate bleeding on probing during the screening period.
   b. Pockets not at adjacent tooth surface sites.
   c. Not to have circumferential periodontal defects where the base of the pocket extended well beyond the proximal surface.
   d. Not to be malpositioned or crowned, if this in any way impeded accurate measurement of PPD or PAL.
   e. No dental implant adjacent to the target tooth.

**Exclusion Criteria:** Subjects with:

1. Diabetes
2. Major recurrent aphthae
3. Stomatitis or related pathoses
4. Need for prophylactic antibiotics prior to dental treatment
5. Oral local mechanical factors that could influence the outcome of the study
6. Orthodontic appliances or any removable appliance that impinged on the tissues being assessed
7. Soft or hard tissue tumors in the oral cavity
8. Five or more caries lesions requiring immediate restorative treatment
9. Severe generalized periodontal disease characterized by extensive tooth mobility and/or extensive alveolar bone loss involving 10 or more teeth
10. Antimicrobial therapy within 30 days before entry into the study
11. History of allergy to chlorhexidine
12. Active periodontal therapy within 12 months of entrance into the study
13. Chronic use of phenytoin, nifedipine, or other calcium channel blockers, cyclosporine, anti-inflammatory drugs or steroids

**Study Design:** Multi center, double-blind, randomized, parallel group study with three treatments as follows:

1. SRP alone

2. SRP + PerioChip™
3. SRP + placebo chip

**Study Procedures:**

## Screening

Subjects were checked for eligibility and a full-mouth periodontal charting was performed.

## Day 0

At this visit, target sites were assigned, clinical indices were measured, and full mouth scaling and root planing was performed. Subjects were randomized to one of two groups:

Group 1 (PerioChip™): Two randomized target sites received a PerioChip™ after scaling and root planing (Treatment 1/Active chip treatment); two additional randomized target sites received no additional treatment following scaling and root planing for the purpose of the maintenance of study blind but, by design, were not included in the efficacy evaluation.

*Reviewer's Comment: Because of the concern about split-mouth design biasing the study results, the sponsor designed the groups in an acceptable manner, which circumvents this problem. The subjects in group 1 received the same follow-up care as the subjects in group 2 (see below - group 2 is the placebo control) so that the two groups would not be treated differently. However, the target sites that received only scaling and root planing in group 1 were not used for efficacy evaluation, since there may be some spill-over effect from the chlorhexidine. Only the sites in group 3 that did not receive a placebo control in the subjects are evaluated for efficacy as the scaling and root planing control. Since the placebo control does not contain active components, it will not possess any carry-over effects to the "scaling and root planing only" sites. Group 2, therefore, contains both treatment 2 and treatment 3, whereas Group 1 contains only treatment 1.*

Group 2 (placebo chip): Two randomized target sites received a placebo chip after scaling and root planing (Treatment 2/Placebo control); two additional randomized target sites received no additional treatment following scaling and root planing (Treatment 3/Scaling and root planing control)

*Comment: One problem with this design is the potential to mask an adverse event associated with some inactive component of the PerioChip™. In Group 2, if the vehicle (gel) has any adverse effect, there is the potential to spill over to the SRP sites. This is not an ideal design - if there is some adverse effect associated with the gel, it may be masked by the placebo group also experiencing it due to exposure to lesser amounts. However, having another group with*

*SRP alone and no chip placed would have removed the blinding of that group, thereby making the results even just for safety comparisons biased.*

Subjects were stratified by smoking status.

Subgingival scaling and root planing was conducted for 1 hour. If supra gingival calculus was present, a separate supra gingival prophylaxis followed. To standardize the SRP procedures across study centers, a training session was conducted for the investigators and their staffs.

Clinical indices including probing pocket depth (PPD) and probing attachment level (PAL), bleeding upon probing (BOP), plaque examination (modified Silness-Loe Plaque Index), staining examination, and gingivitis examination (Loe-Silness Gingival Index) were measured. PPD and PAL were recorded with a manual North Carolina periodontal probe. Examiners were calibrated for PPD and PAL. At baseline, all periodontal measurements taken for potential target sites with the North Carolina periodontal probe were rounded to the nearest ½ mm. The convention for rounding was as follows: for example,

Measurements 5.1 to 5.2 were rounded to 5.0
Measurements 5.3 to 5.4 and 5.6 to 5.7 were rounded to 5.5,
Measurements 5.8 to 5.9 were rounded to 6.0.

## Follow-up visits

After the baseline visit during which the PerioChip™s or placebo chips were placed, there was a scheduled visit at Day 7 for an oral examination and questioning about adverse events. At Week 6, month 3, Month 6, and month 9, clinical indices were measured again.
At Month 3 and Month 6, PerioChip™s or placebo chips were placed in the pockets that previously received chips and that still measured a PPD of 5 mm. (without rounding up) or more. At the 9 month study visit, a routine periodontal prophylaxis was performed on each subject.

**Proposed Statistical Methodology**

A comparison of the test PerioChip™ treatment was to be made with either the *placebo chip +SRP* control or the *SRP only* control.

*Reviewer's comment: It is surprising that there was no record of discussion prior to initiating the pivotal trials about this outcome. Since it is stated that either comparison would be acceptable for a win, that doubles the chances for acceptance. Fortunately, the results demonstrate that PerioChip™ was statistically superior to both the placebo chip group and the SRP-only group.*

For each subject, the changes from baseline with respect to PPD and PAL were to be summarized for each post-baseline visit by taking the means over those target pocket sites where chips had been placed, and also by taking the means over those target pocket sites where chips had not been placed. These means were the variables employed in the statistical analyses that followed.

Separate analyses were performed for each postbaseline visit for the respective comparisons of

- the PerioChip™ treatment against the placebo chip treatment, and
- the PerioChip™ treatment against the SRP control treatment.

Each of the above-mentioned comparisons was to be made by an analysis of covariance model, in which the baseline score was used as a covariate. The analyses for the treatment comparisons used a mean-effects model involving four factors: treatment study center, smoking status, and baseline score. For each postbaseline visit, differences in adjusted mean scores were to be compared. A level of significance of 0.05 (two-tailed) was employed in all statistical comparisons.

## Pivotal Trial Results:

The following section will report the results of both pivotal trials for each of the primary and secondary outcome variables.

### Primary Outcome Variables

The two primary outcomes were improvement in PPD and stabilization of PAL. Statistically significant improvement in PPD was demonstrated between PerioChip™ and both of the control groups in both pivotal trials. For PAL comparisons, not only was the mean PAL reduction from baseline greater in the PerioChip™ group than in both the placebo chip and SRP-only groups in both trials, but in the comparison between PerioChip™ and the placebo chip in study 94-002, the difference was statistically significant.

### PPD

The following tables show mean changes in PPD from baseline that are consistent with PerioChip™ +SRP being significantly greater than SRP alone. Temporally, the PerioChip™ continues to demonstrate improvement through month 9 in Study 94-003. In Study 94-002, the PerioChip™ group demonstrates continued improvement through month 6, and then remains stable for the next 3 months. The SRP groups in both pivotal trials showed an initial improvement at week 6, but lost that improvement over the course of the study. It must be noted, however, that the PerioChip™ was replaced at month 3 and 6 if necessary, whereas the SRP was not repeated after baseline.

## Reduction from Baseline for Pocket Probing Depth (PPD): 94-002

| Treatment | Baseline PPD (mm ± SE) | Mean PPD Reduction from Baseline (mm ± SE) | | | |
|---|---|---|---|---|---|
| | | Week 6 | Month 3 | Month 6 | Month 9 |
| PerioChip™ + SRP | 5.79 ±0.61 n=108 | 0.90 ±0.06 n=107 | 0.95 ±0.07 n=103 | 1.07 ±0.07 n=102 | 1.06 ±0.07 n=101 |
| SRP | 5.69 ±0.58 n=107 | 0.87 ±0.06 n=106 | 0.83 ±0.06 n=103 | 0.80 ±0.07 n=102 | 0.78 ±0.07 n=101 |
| Difference | | 0.03 | 0.11 | 0.27 | 0.29 |
| p-value | | 0.955 | 0.245 | **0.008*** | **0.006*** |
| Placebo Chip | 5.66±0.51 n=107 | 0.75±0.06 n=106 | 0.87±0.07 n=103 | 0.85±0.07 n=102 | 0.73±0.08 n=101 |
| Difference | | 0.16 | 0.08 | 0.22 | 0.34 |
| p-value | | 0.164 | 0.519 | 0.057 | **0.004*** |

## Reduction from Baseline for Pocket Probing Depth (PPD): 94-003

| Treatment | Baseline PPD | Mean PPD Reduction from Baseline (mm ± SE) | | | |
|---|---|---|---|---|---|
| | | Week 6 | Month 3 | Month 6 | Month 9 |
| PerioChip™ + SRP | 5.67 ±0.56 n=117 | 0.52 ±0.05 n=116 | 0.67 ±0.07 n=113 | 0.73 ±0.07 n=111 | 0.84 ±0.08 n=110 |
| SRP | 5.56 ±0.54 n=115 | 0.60 ±0.05 n=113 | 0.64 ±0.06 n=112 | 0.65 ±0.07 n=109 | 0.52 ±0.07 n=107 |
| Difference | | -0.08 | 0.03 | 0.08 | 0.32 |
| p-value | | 0.234 | 0.652 | 0.341 | **0.001*** |
| Placebo Chip | 5.62±0.58 n=115 | 0.53±0.07 n=113 | 0.69±0.06 n=112 | 0.66±0.06 n=109 | 0.65±0.08 n=107 |
| Difference | | -0.01 | -0.02 | 0.08 | 0.18 |
| p-value | | 0.947 | 0.877 | 0.273 | **0.046*** |

***statistically significant at $\alpha = 0.05$**

PAL

The sponsor states that the primary efficacy variables in this study were reduction from baseline of PPD and the stabilization of PAL. The sponsor was aware that a "win" required demonstration of both of these outcomes for both pivotal trials. The sponsor's definition of "stabilization of PAL" is that the loss of attachment in the PerioChip™ group was not to exceed 20% of the loss of attachment in the placebo (i.e., if the placebo group lost a mean of 1.0 mm of attachment, the PerioChip™ group must have lost no more than 1.2 mm to win). It has not been demonstrated that there is any difference between the PAL reduction with PerioChip™ + SRP vs. SRP alone. However, all 3 groups demonstrated a gain in PAL, which is sufficient to claim that the PAL hadn't worsened during the 9 months of the trial.

Because chlorhexidine has never demonstrated an effect on collagen or bone growth, the sponsor did not expect to see an increase in either bone or attachment levels, either of which is accepted for a demonstration of periodontal disease reversal. The sponsor's rationale for including this PAL as a primary outcome variable is to allay the concern that pocket depth reduction may have occurred at the expense of attachment loss worsening. Since the PerioChip™ indication is for reduction of PPD in subjects with chronic adult periodontitis, a net loss of attachment would be counter-productive. To demonstrate improvement in PPD while insuring that attachment will not worsen therefore, was the goal of this trial.

*Reviewer's Comment: "Stabilization of PAL" when viewed in this context, may have better been included as a safety measure, since stabilization or lack of worsening of a condition is generally not a therapeutic claim for elements of periodontal disease.*

**Reduction from Baseline for Periodontal Attachment Level: (PAL): 94-002**

| Treatment | Baseline PAL | Mean PAL Reduction from Baseline (mm ± SE) | | | |
|---|---|---|---|---|---|
| | | Week 6 | Month 3 | Month 6 | Month 9 |
| PerioChip™ + SRP | 5.42 ±1.36 n=108 | 0.58 ±0.08 n=107 | 0.69 ±0.09 n=103 | 0.86 ±0.09 n=102 | 0.84 ±0.08 n=101 |
| SRP | 5.12 ±1.45 n=107 | 0,77 ±0.08 n=106 | 0.71 ±0.07 n=103 | 0.79 ±0.08 n=102 | 0.61 ±0.09 n=101 |
| Difference | | -0.18 | 0.66 | 0.08 | 0.23 |
| p-value | | 0.019 | 0.446 | 0.767 | 0.108 |
| Placebo Chip | 5.12±1.54 n=107 | 0.52±0.08 n=106 | 0.66±0.08 n=103 | 0.69±0.08 n=102 | 0.57±0.08 n=101 |
| Difference | | 0.07 | 0.03 | 0.17 | 0.28 |
| p-value | | 0.899 | 0.819 | 0.284 | **0.035*** |

**Reduction from Baseline for Periodontal Attachment Level (PAL) : 94-003**

| Treatment | Baseline PAL | Mean PAL Reduction from Baseline (mm ± SE) | | | |
|---|---|---|---|---|---|
| | | Week 6 | Month 3 | Month 6 | Month 9 |
| PerioChip™ + SRP | 5.14 ±1.30 n=117 | 0.42 ±0.06 n=116 | 0.56 ±0.07 n=113 | 0.63 ±0.09 n=111 | 0.66 ±0.08 n=110 |
| SRP | 5.15 ±1.42 n=115 | 0.50 ±0.06 n=113 | 0.56 ±0.07 n=112 | 0.62 ±0.07 n=109 | 0.55 ±0.07 n=107 |
| Difference | | -0.08 | 0.00 | 0.01 | 0.10 |
| p-value | | 0.357 | 0.809 | 0.688 | 0.226 |
| Placebo Chip | 5.16±1.43 n=115 | 0.41±0.06 n=113 | 0.56±0.07 n=112 | 0.49±0.07 n=109 | 0.53±0.07 n=107 |
| Difference | | 0.01 | 0.01 | 0.14 | 0.13 |
| p-value | | 0.813 | 0.802 | 0.076 | 0.162 |

*statistically significant at $\alpha = 0.05$

*Examination of Improvement by PD Reduction of ≥ 2.0 mm*

**Classification of % of Sites with PD Reduction≥2.0 mm at Month 9: Study 94-002**

| Treatment | Both sites <2.0 mm | One site≥2.0 mm | Both sites≥2.0 mm | p-value |
|---|---|---|---|---|
| PerioChip™ | 65 (64.4%) | 28 (27.7%) | 8 (7.9%) | |
| Placebo Chip | 80 (79.2%) | 18 (17.8%) | 3 (3.0%) | .029 |
| SRP only | 84 (83.2%) | 13 (12.9%) | 4 (4.0%) | .004 |

OR = 35.6%/20.8% = 1.71 odds of having one or more sites improve by 2.0 mm or more in the Perio chip group compared to placebo chip, and 35.6%/16.9% = 2.11 odds of having one or more sites improve by 2.0 mm or more in the Perio chip group compared to SRP only.

**Classification of % of Sites with PD Reduction≥2.0 mm at Month 9: Study 94-003**

| Treatment | Both sites <2.0 mm | One site≥2.0 mm | Both sites≥2.0 mm | p-value |
|---|---|---|---|---|
| PerioChip™ | 82 (74.5%) | 20 (18.2%) | 8 (7.3%) | |
| Placebo Chip | 83 (77.6%) | 19 (17.8%) | 5 (4.7%) | .447 |
| SRP only | 96 (89.7%) | 10 (9.3%) | 1 (0.9%) | .001 |

OR = 25.5%/10.2% = 2.50 odds of having one or more sites improve by 2.0 mm or more in the Perio chip group compared to SRP alone. It is meaningless to report an Odds ratio for the comparison between the PerioChip™ group and the Placebo Chip group since there was not statistical significance associated with it.

*Stratification by PPD reduction*

The following table is copied from the sponsor's application and includes a breakdown by half-millimeter increments of the PPD reduction from baseline achieved in each study.

**Distribution of Changes in Probing Pocket Depths in Individual Sites at end of Study - Phase 3 Studies**

| Study | PPD Reduction from Baseline | Percent of Pockets | |
|---|---|---|---|
| | | PerioChip™ Pockets | SRP Pockets |
| No. 94-002 | < 1 mm | 39 | 48 |
| | 1- 1.5 mm | 23 | 28 |
| | 1.5 - 2 mm | 16 | 13 |
| | ≥ 2 mm | 22 | 11 |
| No. 94-003 | < 1 mm | 52 | 64 |
| | 1- 1.5 mm | 23 | 22 |
| | 1.5 - 2 mm | 9 | 8 |
| | ≥ 2 mm | 16 | 6 |

This table demonstrates that the number of pockets achieving a PPD reduction from baseline of 2 or more is much greater in the PerioChip™ group than in the SRP only group. At some point between 1 and 2 mm., the numbers are equal, and those pockets that achieved less than a 1 mm PPD reduction are much higher in the SRP alone groups.

Secondary Efficacy Variables

For the secondary efficacy parameters, BOP, Gingival Index, Plaque Index, and Stain Index, only BOP had statistically significant differences between PerioChip™ and either of the two control groups.

**BOP**

The clinical evaluation of change from baseline in BOP is summarized in the table below. All patients experienced BOP at baseline. In study 94-002, the difference between the number of sites that had BOP in the PerioChip™ group achieved statistical significance when compared to placebo chip as well as when compared to SRP alone. In study 94-003, on the other hand, no statistically significant difference was demonstrated between the PerioChip™ group and either the placebo group or SRP alone.

BOP at Month 9

| | Treatment | Neither site BOP | One site BOP | Both sites BOP | p-value |
|---|---|---|---|---|---|
| 94-002 | PerioChip™ | 31 (28.7%) | 39 (36.1%) | 38 (35.2%) | |
| | Placebo Chip | 22 (20.6%) | 35 (32.7%) | 50 (46.7%) | 0.046 |
| | SRP alone | 19 (17.7%) | 37 (34.6%) | 51 (47.7%) | **0.018*** |
| 94-003 | PerioChip™ | 13 (11.1%) | 44 (37.6%) | 60 (51.3%) | |
| | Placebo Chip | 13 (11.3%) | 36 (31.3%) | 66 (57.4%) | 0.443 |
| | SRP alone | 11 (9.6%) | 33 (28.7%) | 71 (61.7%) | 0.146 |

***statistically significant at $\alpha = 0.05$**

The sponsor performed an analysis of the results by observation period, which provided the following information: In study 94-002, the distribution of bleeding sites showed that PerioChip™ sites experienced fewer bleeding episodes compared to both control groups (SRP alone and placebo chip sites) at Week 6 ($p < .05$), Month 6 ($p < .05$) and Month 9 ($p < .05$). In study 94-003, Week 6 was the only time point in which subjects who received PerioChip™ experienced fewer bleeding episodes compared to both control groups; however, this result did not reach statistical significance. At Month 6, the PerioChip™ plus SRP group experienced significantly **more** bleeding episodes compared to the SRP alone group ($p = 0.062$).

**Gingival Index**

The results provide mixed trends in the gingival index comparisons between the test and control groups; however, the only comparison that yielded a statistically significant difference was PerioChip™ vs. SRP alone at Week 6 in Study 94-002.

At most time points in Study 94-002, the mean reduction in the Gingival Index was greater in the PerioChip™ group than in the control groups (SRP alone and placebo chip). The comparative analysis revealed a significant result only for the PerioChip™ sites versus the SRP alone sites at Week 6 ($p = 0.037$). There were no other significant differences between treatment groups.

At no time point in Study 94-003 was the mean reduction in the Gingival Index greater in the PerioChip™ group than in either of the control groups (SRP alone and placebo chip groups). The comparative analysis revealed no significant differences between treatment groups.

**Gingival Index**

| Study | Group | Baseline | Week 6 | Month 3 | Month 6 | Month 9 |
|---|---|---|---|---|---|---|
| 94-002 | PerioChip™ | 1.64 | 1.14 | 1.19 | 1.17 | 1.26 |
| | Placebo Chip | 1.64 | 1.22 | 1.24 | 1.28 | 1.24 |
| | SRP alone | 1.64 | 1.27 | 1.20 | 1.22 | 1.27 |
| 94-003 | PerioChip™ | 1.37 | 1.29 | 1.29 | 1.29 | 1.30 |
| | Placebo Chip | 1.46 | 1.29 | 1.32 | 1.38 | 1.36 |
| | SRP alone | 1.48 | 1.32 | 1.28 | 1.27 | 1.36 |

**Plaque Index**

Like the gingival index results, the plaque index results provide mixed trends in the comparisons between the test and control groups; however, none of the differences were statistically significant, so the overall conclusion is that there was no difference demonstrated.

In Study 94-002, the general trend in the plaque index comparisons between the test and control groups reveal a greater reduction in the plaque index in the PerioChip™ group than in the control groups. At all time points, the mean reduction in the Plaque Index was greater in the PerioChip™ group than in the control groups (SRP alone and placebo chip). However, the comparative analysis revealed no significant differences.

In Study 94-003, only Month 3 results showed a greater mean reduction in plaque index in the PerioChip™ group than in both of the control groups. At all of the other time points, one of the control groups had a mean difference in plaque index that was greater than the PerioChip™ group's. None of these differences reached statistical significance.

**Plaque Index**

| Study | Group | Baseline | Week 6 | Month 3 | Month 6 | Month 9 |
|---|---|---|---|---|---|---|
| 94-002 | PerioChip™ | 1.30 | 1.03 | 1.11 | 1.12 | 1.23 |
| | Placebo Chip | 1.23 | 1.11 | 1.03 | 1.09 | 1.17 |
| | SRP alone | 1.22 | 1.07 | 1.04 | 1.08 | 1.19 |
| 94-003 | PerioChip™ | 1.17 | 1.07 | 1.07 | 1.18 | 1.13 |
| | Placebo Chip | 1.21 | 1.20 | 1.21 | 1.33 | 1.16 |
| | SRP alone | 1.22 | 1.13 | 1.16 | 1.20 | 1.19 |

**Staining Index**

Staining was selected as another secondary efficacy variable, because it is a documented adverse event resulting from chlorhexidine rinse use. Calling this an efficacy variable is probably a misnomer, as there was never a hypothesis that chlorhexidine chip placement would reduce stain. Rather, it was monitored to determine whether the label should warn of staining as an adverse event. Both pivotal trials exhibited no observable stains on supragingival tooth surfaces at baseline and there was little change in the SI over the treatment period in any of the treatment groups. Due to the lack of any significant occurrence of staining, no warning is required on the label.

## Adverse Events

### Adverse Events Frequency Reported by Five or More Subjects Studies 94-002 and 94-003

| | PerioChip™ | | Placebo Chip | |
|---|---|---|---|---|
| | N | % | N | % |
| All patients | 225 | | 222 | |
| All Patients with Adverse Events | 193 | 85.8 | 189 | 85.1 |
| Body as a Whole | | | | |
| Influenza-like symptoms | 17 | 7.6 | 21 | 9.5 |
| Back pain | 15 | 6.7 | 25 | 11.3 |
| Pain | 11 | 4.9 | 11 | 5.0 |
| Allergy | 9 | 4.0 | 13 | 5.9 |
| Cardiovascular, General | | | | |
| Hypertension | 5 | 2.2 | 6 | 2.7 |
| Central & Peripheral Nervous System | | | | |
| Headache | 61 | 27.1 | 61 | 27.5 |
| Gastrointestinal | | | | |
| Toothache | 114 | 50.7 | 92 | 41.4 |
| Tooth disorder | 14 | 6.2 | 15 | 6.8 |
| Gum hyperplasia | 8 | 3.6 | 5 | 2.3 |

| | | | | |
|---|---|---|---|---|
| Dyspepsia | 7 | 3.1 | 6 | 2.7 |
| Stomatitis ulcerative | 5 | 2.2 | 1 | 0.5 |
| Musculoskeletal System | | | | |
| Myalgia | 9 | 4.0 | 9 | 4.1 |
| Arthralgia | 7 | 3.1 | 13 | 5.9 |
| Arthrosis | 6 | 2.7 | 4 | 1.8 |
| Tendinitis | 5 | 2.2 | 1 | 0.5 |
| Reproductive Disorders, Female | | | | |
| Dysmenorrhea | 7 | 3.1 | 13 | 5.9 |
| Resistance Mechanism | | | | |
| Abscess | 13 | 5.8 | 13 | 5.9 |
| Respiratory | | | | |
| Upper resp tract infection | 64 | 28.4 | 58 | 26.1 |
| Sinusitis | 31 | 13.8 | 29 | 13.1 |
| Bronchitis | 14 | 6.2 | 7 | 3.2 |
| Pharyngitis | 8 | 3.6 | 5 | 2.3 |
| Coughing | 6 | 2.7 | 7 | 3.2 |
| Rhinitis | 6 | 2.7 | 11 | 5.0 |

Under the above listing "Tooth disorder," the sponsor includes lost PerioChip™s. The sponsor was queried as to a specific breakdown of the lost PerioChip™s, and responded with the information provided in the following table:

## All Subjects who reported Tooth Disorder: Study 94-002

| Patient Number | Treatment | Description | Date Chip Placed | Date Reported |
|---|---|---|---|---|
| | Placebo | Patient reported chip came out | 9/27/94 | 9/27/94 |
| | PerioChip™ | Potential lost chip due to use of dental floss | 11/09/94 | 11/09/94 |
| | Placebo | Lost 1 chip | 11/10/94 | 11/12/94 |
| | PerioChip™ | Lost 1 chip | 11/10/94 | 11/17/94 |
| | Placebo | Patient reported a piece of chip came out | 11/30/94 | 12/04/94 |
| | PerioChip™ | Lost 1 chip | 12/12/94 | 12/17/94 |

## All Subjects who reported Tooth Disorder: Study 94-003

| Patient Number | Treatment | Description | Date Chip Placed | Date Reported |
|---|---|---|---|---|
| | Placebo | Patient states possibility of a lost PerioChip™ | 08/16/94 | 08/16/94 |
| | Placebo | Patient claims to have lost part of a chip | 08/05/94 | 08/08/94 |

Refer to the Adverse Events subsection of the Discussion section of this review for discussion and recommendations regarding the above tables.

**Demographics**

Six hundred sixty subjects were enrolled in Phase 3 clinical trials, 213 in the split mouth study and 447 in the parallel group U.S. studies. The demographic profile of subjects is listed in the table below. The mean age was between 46 and 47 years, and there were about equal proportions of men and women. There were no statistically significant differences between the PerioChip™ and the placebo chip with respect to any demographic variables in the U.S. studies.

**Baseline Demographic Characteristics**

| Baseline Characteristic | | No. 94-002 | | No. 94-003 | |
|---|---|---|---|---|---|
| | | PerioChip™ | Placebo Chip | PerioChip™ | Placebo Chip |
| Sex | Male (n) | 52 | 50 | 50 | 55 |
| | Female (n) | 56 | 57 | 67 | 60 |
| Age | Minimum | | | not reported | not reported |
| | Maximum | | | not reported | not reported |
| | Mean | 46.8 (9.0) | 46.5 (10.6) | 46.8 (9.0) | 46.8 (10.0) |
| Race | Caucasian | 87 | 77 | 83 | 89 |
| | Black | 16 | 27 | 27 | 15 |
| | Initial pocket depth (mm) | 5.73±0.60 | 5.79±0.61 | 5.69±0.56 | 5.58±0.54 |

***Subgroup analysis***

To investigate any effect from demographic variables, subgroups of subjects were formed by gender, race (white vs. nonwhite), age (< 50 years, ≥ 50 years), and smoking status. The data of the two pivotal trials were pooled to provide a larger sample size to detect a significant interaction. For each subset, the analysis performed on PPD reduction from baseline was done using ANCOVA. At the 0.10 level for the interaction term, the only statistically significant interaction term was between the PerioChip™ group and SRP-only group for smoking status. For all subsets, the reduction of PPD was greater for the PerioChip™ than either the placebo chip or SRP only groups. This reduction was more pronounced for PerioChip™ males than PerioChip™ females, PerioChip™ whites than PerioChip™ nonwhites, PerioChip™ nonsmokers than PerioChip™ smokers, and PerioChip™ subjects ≥ 50 years old than PerioChip™ subjects < 50 years old.

*Age*

The differences between the reduction in PPD in all treatment groups at all time points was similar in subjects in the age subgroups < 50 years of age and ≥ 50 years. No significant treatment-by-age interactions were demonstrated.

*Race*

The reduction in PPD was greater at all time points among whites than among non-whites in both the PerioChip™ group and in the control groups. However, there were no significant interactions between the two subgroups and treatment at any time point.

*Gender*

PerioChip™ treatment was similarly effective in men and women. No significant treatment-by-gender interactions were demonstrated at Month 9.

*Smoking status*

In the two pivotal trials, subjects were stratified according to their smoking status. Approximately 35% of the subject population were smokers. The average baseline pocket depth was similar in both smoking and nonsmoking subgroups. At Week 6 and Month 3, the reduction in PPD from baseline was similar in both subgroups for all treatments. At Month 6 and Month 9, the reduction of PPD from baseline was more pronounced in the PerioChip™ nonsmokers than in the PerioChip™ smokers. At Month 9, among nonsmokers, the difference in PPD reduction between the PerioChip™ and SRP alone was 0.39 mm, and between the PerioChip™ and placebo chip, 0.32 mm. Among the smoking subgroup, the difference in PPD reduction between the PerioChip™ and SRP alone was 0.14 mm, and between the PerioChip™ and placebo chip, 0.15 mm. In spite of these differences, in both smoking and nonsmoking subgroups, the PPD reduction was greater in the PerioChip™ group than in the control groups, and no interactions between the two subgroups and treatments were noted. In conclusion, there were no significant interactions between smoking status and treatment, although in all groups the reduction in PPD was greater in non-smokers than smokers.

*Reviewer's Comment: In the U.S. studies, about 35% of the patient population were smokers, while in the European/Israeli study, smokers using more than 10 cigarettes per day were excluded. In the analysis of the non-smoking subgroups in the US studies, the difference in PPD reduction from baseline for the PerioChip™ versus SRP-only group was 0.39 mm, which closely approximates the European/Israeli results.*

**Discussion:**

The sponsor's approach to the development of this drug has been logical and thoughtful. Comments that were made by the agency and supplied to the sponsor were thoroughly considered. The sponsor used the information gained in preliminary completed trials to plan the next trial. Although the Phase 2 trials employed protocol design elements that were not capable of demonstrating definite conclusions - due to small group sizes making significance difficult to achieve, and a split mouth design which may have washed out some of the effect

due to cross-over effect - they were able to establish trends that were sufficient to support continuing drug development with conclusive studies. They also used the results of earlier trials to settle on a final dosing after their initial hypothesis that using two chips one week apart proved to impact negatively on efficacy. The discussions with the agency proved productive in helping to establish the primary and secondary endpoints, and establishing the correct design of the trial.

In this section of the review, an analysis of the results of the trials provided in the NDA submission is provided, focusing primarily on the 2 pivotal trials. The discussion is being divided into subsections, including choice of efficacy variables, clinical significance of PPD changes, gingivitis and plaque indexes, bleeding on probing, dosing and dosing interval, and labeling implications.

*Choice of Efficacy Variables and relationship to periodontitis*

The sponsor's proposed indication for PerioChip™ is

More specifically, in the proposed label under *Indications and Usage*, the statement reads

Although PerioChip™ has demonstrated statistically significant reduction of pocket depth which would be useful in a periodontal maintenance program, this outcome alone is not sufficient to claim . Published literature, including guidelines put out by the Task Force on Design and Analysis, American Dental Association, and the American Academy of Periodontology, all state that either bone loss or attachment level must be primary outcome variables in any trial of drugs to treat or arrest periodontitis[1]. By definition, periodontitis is one of the periodontal diseases that occurs when changes in attachment of the tooth, which includes both the soft tissue attachment (periodontal fibers) and the alveolar bone show degeneration. Bone levels were not assessed at any point in the clinical trials for PerioChip™, and attachment levels were measured for use only as a safety outcome, i.e., the loss of attachment in the PerioChip™ group was not to exceed 20% of the loss of attachment in the placebo. Clearly, improvement in either bone or attachment levels was not demonstrated. As such, treatment of periodontitis is not a valid claim. Although inclusionary criteria for the pivotal trials did not include specific attachment levels or bone loss, "at least four teeth with probing depth of 5 - 8 mm" was mandated. As would be expected, the mean baseline PAL was 5.2 mm. for the pivotal trials, which, coupled with the baseline PPD, supports the premise that all of the subjects did in fact have some degree of currently active periodontitis. Labeling will therefore, need to be altered to clarify that the chip may be helpful as an adjunct to scaling

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[1]References: 1. Imrey, Chilton, Pihlstrom et al, Proposed guidelines for American Dental Association acceptance of products for professional, non-surgical treatment of adult periodontitis, J. Periodont Res 1994: 29: 348-360.

and root planing procedures in patients with periodontitis, but to be accurate must eliminate references to the *treatment* of periodontitis.

At first appearances, it is inconsistent that the active treatment arms were able to demonstrate consistently significant improvement in PPD, but not in PAL. In addition, the gingivitis index results were nearly identical between groups. It followed that if the reduction in bacteria at the base of the pocket results in reduction of PPD, then PAL should improve as well; if the reduction in PPD results from shrinkage of the marginal gingiva, one would expect the gingival index to improve. The sponsor, who was queried about the apparent inconsistencies, formally responded to the request for information.

The sponsor correctly points out that all subjects enrolled in the pivotal trials, regardless of group assignment, received SRP, which effectively results in an across the board reduction in gingival inflammation. The sponsor states that the PerioChip™ therapy reduces the bacterial load in the periodontal pocket, thereby arresting the inflammatory process at the base of the pocket. Thus, the Gingival Index, which is indicative primarily of gingival inflammation (as measured by swelling, redness and bleeding upon stimulation of the gingival crevice) was not significantly changed after the baseline examination. On the other hand, both PPD and PAL which are primarily affected by changes at the pocket base, improved to a similar extent. According to the sponsor, the smaller decrease in the magnitude of change observed for PAL compared to PPD (and resulting lack of statistical significance in 3 of the 4 comparisons) results from two factors: (1) greater variability in the measurement of PAL compared to PPD and (2) the additional component of PPD reduction that results from the apical positioning of the gingival margin due to tissue shrinkage. The sponsor's definition of success in the primary outcome variable for PAL as "stabilization" was probably an attempt to err on the conservative side of expected effect. Certainly, although the magnitude of change in PAL is not as great as is seen with PPD, the trend is quite strong and supportive. The sponsor's explanation is reasonable.

*Clinical Significance of PPD changes*

It is difficult to gauge the clinical significance of shrinking a periodontal pocket. The ultimate therapeutic concern of periodontal disease is halting periodontitis, i.e., destruction of the connective tissue and bone that ultimately maintains the health and function of the teeth. The sponsor has made it clear that chlorhexidine, as delivered through the chip system, does not have a therapeutic effect on attachment or bone. Probably the benefit of pocket depth reduction is that it facilitates an individual's access to the area for removing accumulated subgingival plaque. Since plaque is the etiology for periodontal diseases, its reduction should help to prevent progression of periodontitis.

Although the differences in PPD reduction between the PerioChip™ and SRP alone groups were statistically significant in both pivotal studies, this alone is not sufficient to establish

clinical utility - a therapeutic benefit should be achieved as well. During an meeting with the agency, the sponsor defined clinical significance as a mean additional reduction in PPD of 0.4 mm. when comparing the group which received SRP plus PerioChip™ to the group which received SRP alone. At a subsequent meeting, the sponsor stated that a PPD reduction of 2 mm. or more should be analyzed on a per patient basis. The sponsor's reasoning is that a pocket reduction of 2 mm or more can be readily measured by the periodontist or general dentist and often impacts on the patient prognosis and treatment plan.

Using the first criterion of clinical significance, the actual reduction in PPD of the SRP plus PerioChip™ group above and beyond SRP alone is 0.29 mm and 0.32 respectively as reported from pivotal trial 94-002 and 94-003; the actual reduction of the SRP plus PerioChip™ group above and beyond SRP plus placebo chip is 0.34 mm and 0.18 mm respectively as reported from pivotal trial 94-002 and 94-003. An analysis of the percentage of sites with PPD improvement of 2 mm or more from baseline in the two US studies demonstrated that in the PerioChip™ group it was approximately twice as great as in the SRP alone group (Study 94-002: OR = 1.93, $p<0.05$; Study 94-003: OR = 1.91, $p<0.01$). These two interpretations both support the notion that PerioChip™ is a marginally effective product at reducing pocket probing depth.

The overall mean value for reduction of SRP beyond SRP alone or SRP and placebo is approximately 0.3 mm., which falls short of the sponsor's target value of 0.4 mm. Scaling and root planing is a very effective treatment for reducing pocket depths, as demonstrated both by published literature and the results of this trial which produced an improvement of approximately 1 mm.[2] A statistically significant additional improvement in pocket depth above and beyond this value demonstrates effectiveness of the drug; however, evaluating the importance of a 0.3 mm improvement is difficult. Because this value is a mean, it does not reflect how many subjects in the trial had a larger improvement to offset those who performed poorer. The sponsor's next analysis examined that.

The sponsor's analysis of subjects who improved by 2 mm or more was helpful as this result would affect treatment planning, and may result in an avoidance of more aggressive treatment such as surgery to achieve a similar result. This analysis, which resulted in a statistically significant difference between groups, also supports marginal effectiveness of PerioChip™. In the first pivotal study, 34% of subjects demonstrated improvements at one or both sites of greater than 2.0 mm in the PerioChip™ plus SRP group as compared to 18% of subjects in the SRP only group; in the second study, 25% of subjects demonstrated improvements at one or both sites of greater than 2.0 mm in the PerioChip™ plus SRP group as compared to 13% of

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[2]According to a review article examining non-surgical pocket therapy which was published as a part of the proceedings of the 1996 World Workshop in Periodontics, "pockets with an initial depth of 4 to 6 mm had a mean gain of 0.55 mm, and those ≥ 7 mm exhibited the greatest gain in mean clinical attachment level at 1.29 mm. (Cobb, Non-Surgical Pocket Therapy: Mechanical, Ann Periodontol 1996:1:443-490).

subjects in the SRP only group. The calculated odds ratio, although statistically significant, has a respective value of 1.93 and 1.91. Generally, statistically significant odds ratio of greater than 1.0 support a significant difference between groups; however, odds ratios of less than 2.0 are considered inconclusive of supporting a cause and effect relationship. In addition, one of the groups, placebo chip plus SRP, when compared to PerioChip™ plus SRP, showed no significant difference (25% in PerioChip™ group vs. 23% in the Placebo Chip group for the percentage of subjects who demonstrated one or both sites as having reductions of 2.0 mm or more).

Initially, there was some concern regarding the reporting of the endpoint, "subjects whose PPD improved by 2 mm or more." The primary endpoint measures as stated in the protocol of the pivotal trials were 1) the Month 9 results of reduction from baseline of PPD and 2) no worsening of PAL by ≥ 20%. For each pivotal trial, the difference in mean values of PPD between the PerioChip™ + SRP group and the SRP alone group was examined for statistical and clinical significance. The decision to conduct statistical analyses of the percentage of subjects in each group who gained more than 2 mm. of PAL was apparently made at some point after the trials were initiated. It appears unlikely that this analysis was the result of data dredging, because the 1994 ADA publication on acceptance of products for professional, non-surgical treatment of adult periodontitis (Imrey PB, Chilton NW, et al. *Proposed guidelines for American Dental Association acceptance of products for professional, non-surgical treatment of adult periodontitis, J Periodont Res 1994: 29: 348-360*) discussed use of this 2 mm. value for PPD as a useful measurement as follows: "Another acceptable approach is to summarize post-therapy behaviors of these variables by the proportions (%) of sites which exceed one or more specified thresholds of change, e.g. 2 mm of attachment loss, 1 mm. of attachment gain. Therapeutic activity may then be assessed by comparing such proportions observed after product use with those observed in controls." Note that this publication occurred between the times of initiation of this trial, and submission of the NDA. In addition, it is helpful to the dental practitioner to include this analysis of PPD in the label, as it will have more value to affect clinical decisions (by impacting on the patient prognosis and treatment plan) than simply a report of mean values. Although this endpoint measure was not listed *a priori* as primary, because it was demonstrated in both trials with a strong degree of statistical significance, its inclusion on the label is acceptable.

Actisite™, a tetracycline impregnated fiber, was approved by CDER in 1994 for the indication, "as an adjunct to scaling and root planing for reduction of pocket depth and bleeding on probing in patients with adult periodontitis." Actisite™ demonstrated an additional reduction in PPD of approximately 0.67 mm. over the control group that had SRP only. However, it must be noted that Actisite™ trials enrolled subjects with a mean pocket depth of 7.2 mm. in one of the trials, and 6.4 mm. in the other (as compared to 5.6 mm. to 5.8 mm baseline pocket depth in PerioChip™'s pivotal trials). The Actisite™ label states that probing depth reductions were greater in deep (≥7 mm) than in moderate (≤ 6 mm) sites. Even if Actisite™ and PerioChip™ are equally effective in reducing PPD, a smaller reduction would be expected in the

PerioChip™ study due to the lesser degree of disease at baseline. It is not possible to extrapolate data to different initial pocket depths to judge whether Actisite™ is more effective than PerioChip™, given the usual problems with cross-study comparisons such as the differences in populations being tested, clinical investigators, and protocols. Actisite™ was never examined for percent of sites that improved greater than 2.0 mm, so comparisons cannot be made with those results. Based upon the mean PPD values reported for both Actisite™ and PerioChip™, approval of PerioChip™ would be consistent with the decision to approve Actisite™.

The additional labeling which reports the results as a percentage of subjects who achieved ≥ 2.0 mm of PPD improvement is beneficial to practitioners as a useful way to gauge clinical efficacy (Refer to discussion in prior paragraph). The review of Actisite™ was conducted prior to the publication of the Task Force on Design and Analysis' recommendations of this analysis, which explains its absence in Actisite™'s results. It is strongly recommended that future drug products submitting guidance from the agency be advised to include this method of data analysis as a part of the statistical plan.

*Gingivitis and Plaque Indexes*

Because of the sponsor's premise that the PPD is reduced due to less inflammation as a result of less bacteria surrounding the tooth at the gumline, it is somewhat inconsistent that the differences between groups for the plaque and gingivitis indexes were not greater. The gingivitis index results showed one significant time point (6 weeks) at which the reduction in mean GI was greater in the PerioChip™ group versus the SRP alone group. However, the trend in the rest of the points were split between a slight reduction and a slight gain in mean GI for the PerioChip™ group - one would conclude an overall lack of effect. Similarly, the plaque index results provide mixed trends in the comparisons between the test and control groups - one of the studies tended towards a plaque-reduction in the PerioChip™ group whereas the other study resulted in more plaque reduction from the control groups. Once again, the overall conclusion would be a lack of effect on supragingival plaque from PerioChip™.

*Bleeding On Probing*

BOP, which was measured as a secondary efficacy outcome, is a cardinal sign of gingival inflammation. BOP should correlate very closely with the gingival index, which measures inflammation by visually gauging redness, edema, and bleeding. In study 94-002, the difference between the number of sites that had BOP in the PerioChip™ group achieved statistical significance when compared to placebo chip as well as when compared to SRP alone. In study 94-003, on the other hand, no statistically significant difference was demonstrated between the PerioChip™ group and either the placebo group or SRP alone. When separated by observation period, a further analysis of the results provided the following information: In study 94-002, the distribution of bleeding sites showed that PerioChip™ sites experienced fewer

bleeding episodes compared to both control groups (SRP alone and placebo chip sites) at Week 6 ($p < .05$), Month 6 ($p < .05$) and Month 9 ($p < .05$). In study 94-003, Week 6 was the only time point in which subjects who received PerioChip™ experienced fewer bleeding episodes compared to both control groups; however, this result did not reach statistical significance. At Month 6, the PerioChip™ plus SRP group experienced significantly more bleeding episodes compared to the SRP alone group ($p = 0.062$). **Given the equivocal nature of these results, the claim that PerioChip™ reduces bleeding on probing is not supported.**

*Calculus*

Because accumulation of supragingival calculus is an adverse event associated with use of chlorhexidine rinses, it would have been prudent to have designed the pivotal trials to score calculus with one of the indexes available at the end of the 9 months and make a comparison between the groups. Unfortunately, this was not done, and discussions with the Agency have not included this concern. The use of a chlorhexidine chip for 7 - 10 days, placed subgingivally, is much different than the oral rinses, which are used twice daily chronically and come in direct contact with the tooth surfaces. Although it would be of interest to answer this question definitively with a trial, the evidence does not warrant requiring the sponsor to conduct another pivotal trial prior to approval. A post-approval, Phase 4 trial could remove the concern about calculus accumulation with use of PerioChip™; however, the decision of the clinical review team is that this is not necessary, given the totality of information.

*Labeling Implications*

It is apparent from the collective results of these trials that the action of PerioChip™ is limited to its effect on pocket probing depth only. The inability of PerioChip™ to demonstrate significant plaque, gingivitis, or BOP improvements over placebo is consistent and supports this conclusion. Although chlorhexidine gluconate rinse has been approved "for the treatment of gingivitis as characterized by redness and swelling of the gingivae, including gingival bleeding upon probing" (Approved label for Peridex®: NDA 19028), this is based upon it ability to act locally at the free gingival margin and supragingival tooth surfaces. Just as chlorhexidine rinses have not been shown to penetrate into the pockets of the teeth, it appears as though the subgingivally-placed PerioChip™ does not exert an effect on plaque and gingivitis above the gumline. Therefore, it should be clarified in the labeling that PerioChip™ does not help to improve gingivitis, bleeding upon probing, and does not reduce supragingival plaque.

*Dosing and Dosing Interval*

The PerioChip™ containing 2.5 mg chlorhexidine releases chlorhexidine into the periodontal pocket. Average concentrations of approximately 2000 $\mu$g/mL at 2 hours to 125 $\mu$g/mL at 8 days were measured in the gingival crevicular fluid. Chlorhexidine at this concentration inhibits 99% of the subgingival bacteria. 2.5 mg of chlorhexidine was selected as the dose

because: 1) it will provide for the maintenance of effective antimicrobial concentrations in the periodontal pocket for 7 - 10 days, but 2) it will not exceed safe concentrations of chlorhexidine as determined by studies with chlorhexidine mouthrinse.

In the Phase 2 study, the dose response of PerioChip™ was evaluated by the administration of two PerioChip™s at an interval of one week. There was no significant difference in clinical variables between the two treatments, one or two active PerioChip™s. There was even a trend for a slight advantage of one chip over two, suggesting interference with tissue healing as a result of the additional physical manipulation within the one week period.

Since the effects of locally delivered chlorhexidine in this study were evident for approximately 3 months, and since an administration interval of 3 months would correspond to the common periodontal recall interval in the US of 3 months, it was determined that the Phase 3 clinical program would study the administration of PerioChip™ to periodontal pockets ≥ 5 mm. every 3 months.

The Phase 3 European/Israeli study protocol design allowed for insertion of PerioChip™s in any eligible tooth site in a randomly selected upper quadrant. As a result, the number of chips inserted in a single subject quadrant, at any visit, ranged from , with an average of 4. There were no serious adverse events reported in this study that were considered treatment-related. Percentage-wise, there were fewer adverse events reported overall in this trial than in the pivotal trials (55% of all subjects reported any adverse event in the non-pivotal trial; 85% of subjects reported any adverse event in the pivotal trials), as well as less tooth or gum disorder adverse events (63% in the pivotal vs. 50% in the non-pivotal trials) Below is a table of the subject distribution of the number of PerioChip™ insertions at a visit.

**Subject Distribution of Number of PerioChip™s Inserted (Protocol 92-002)**

| Number of Subjects | Number of PerioChip™s Inserted |
|---|---|
| 92 | 1 - 4 |
| 42 | 5 - 7 |
| 21 | ≥ 8 |

The sponsor failed to address the maximum number of PerioChip™s to be placed per visit in the submission or on the proposed label. Follow-up questioning of the sponsor provided the response that the maximum is 8 chips, citing the European data as evidence of efficacy and safety with that number of chips. It appears to be a reasonable number since efficacy was established with two chips placed per visit in both pivotal trials, and 15% of the subjects in the European Phase 3 trial received 8 chips or more. There is no reason to believe that separate

examination of studies results with 3, 4, 5, 6, 7, and 8 chips would be necessary to support labeling of up to 8 chips. In terms of safety, however, the pharmacokinetics study examined a maximum of only 4 chips. Although the sponsor has requested the use of 8 PerioChip™s at any one time, in vivo pharmacokinetc information was only provided for the use of 4 PerioChip™s. As a result of this concern, additional information from the literature as to the absorption of chlorhexidine following oral administration was requested. The biopharmaceutics reviewer concluded that the information provided by the sponsor in combination with the *in vivo* data are sufficient to support the use of up to 8 PerioChip™s at any one time in a patient. In terms of clinical efficacy and adverse event monitoring, there is no serious concern about approving labeling for a maximum of 8 chips per visit from the clinical review.

*Effect of Multiple Chip Placement*

Further analyses of the results of the two pivotal trials were conducted by the Division to examine the effects of multiple chips, and whether significant effects were achieved if no significant effect was achieved with one chip after a 3 month period. Because the group sizes were greatly reduced to create the additional cells, statistical significance was only reached in 3 of the comparisons. However, the magnitude and trend of the effects were very similar to the overall comparisons.

**Report of PPD outcome stratified by number of chips placed: Study 94-002**

| | | | PPD (mm.) | Improvement in PPD (mm.) | | |
|---|---|---|---|---|---|---|
| Treatment | N | # Chips | Baseline | Month 3 | Month 6 | Month 9 |
| Placebo | 59 | 1 | 5.37 | 1.42 | 1.43 | 1.14 |
| | 14 | 2 -2nd at 3 mos | 5.82 | 0.57 | 1.49 | 1.01 |
| | 17 | 2 -2nd at 6 mos | 5.57 | 1.33 | 0.41 | 0.66 |
| | 57 | 3 | 6.01 | 0.29 | 0.27 | 0.26 |
| PerioChip™ | 63 | 1 | 5.44 | 1.48 | 1.62 | 1.43 |
| | 25 | 2nd at 3 mos | 5.93 | 0.56 | 1.65 | 1.11 |
| | 18 | 2nd at 6 mos | 5.70 | 1.38 | 0.47 | 0.91 |
| | 57 | 3 | 6.13 | 0.36 | 0.35 | 0.57 |

**Report of PPD outcome stratified by number of chips placed: Study 94-003**

| | | | PPD (mm.) | Improvement in PPD (mm.) | | |
|---|---|---|---|---|---|---|
| Treatment | N | # Chips | Baseline | Month 3 | Month 6 | Month 9 |
| Placebo | 57 | 1 | 5.07 | 1.29 | 1.38 | 1.20 |
| | 25 | 2 -2nd at 3 mos | 5.61 | 0.34 | 1.01 | 0.73 |
| | 18 | 2 -2nd at 6 mos | 5.38 | 1.25 | 0.31 | 0.79 |
| | 76 | 3 | 5.99 | 0.21 | 0.13 | 0.26 |
| PerioChip™ | 60 | 1 | 5.24 | 1.30 | 1.39 | 1.26 |
| | 21 | 2nd at 3 mos | 5.64 | 0.41 | 1.33 | 1.38 |
| | 19 | 2nd at 6 mos | 5.37 | 1.17 | 0.37 | 0.75 |
| | 68 | 3 | 6.08 | 0.08 | 0.10 | 0.38 |

There was no real pattern here, other than the mean baseline PPD of the group that required 3 chips was the highest and the group that only required one chip to reduce its PPD to 5.0 mm or less had the smallest PPD measurement at baseline. This finding is consistent with the protocol requirement that those subjects with pocket depths greater than 5 mm at each evaluation receive a chip (i.e., the more diseased subjects receive more chips, rather than subjects receiving more chips develop deeper pockets). In Study 94-002, the group that required 3 chips had a significant improvement over the group that received three placebo chips (difference of .31 mm, statistical significance reached) and similarly, in Study 94-003, this same comparison yielded an improvement of .12 mm (which was not statistically significant). This is consistent with other results demonstrating that the group receiving PerioChip™ improved more than the group receiving placebo.

Adverse Events

From the outset, it must be stated that the safety of the topical use of chlorhexidine in the oral cavity has been thoroughly reviewed during the review of Peridex oral rinse (NDA 19-028). Chlorhexidine has also been approved through the NDA process for surgical hand scrubs, health-care personnel hand washes and patient preoperative skin preparations (Refer to *Background and Regulatory History* section of this review). Although the form of chlorhexidine and its site of action in the PerioChip™ is somewhat different than in Peridex rinse, it must be noted that simultaneous placement of up to 8 chips as the manufacturer has suggested results in total exposure to chlorhexidine in PerioChip™ that is a fraction of that in Peridex, an approved drug. For this NDA submission, thorough reviews of chemistry, toxicology, and pharmacokinetics were conducted. These results have been summarized in this review, although the primary focus of this discussion will be any topical adverse events associated with the chip, since that is unique to this product over the other approved

chlorhexidine-containing products.

Adverse event data were presented from all of the human clinical studies conducted. In addition to the two pivotal US studies (94-002 and 003), data from the European/Israeli Phase 3 trial (92-002), the Phase 2 split-mouth designed study (91-013), a Phase 1, parallel-group study, (No.89-001) and two pharmacokinetic studies, (No. 95-000 and No. 95-000A) were reported. Because of the way the pivotal trials were designed, subjects in the SRP-only group still received either 2 PerioChip™s or 2 placebo chips on the side opposite the SRP only sites. The SRP-only sides of the mouth were included in the safety evaluations for both the PerioChip™ and placebo chip groups, whereas for efficacy, only the SRP-only sites in subjects in the Placebo chip group were evaluated. As was discussed earlier in this review, this is an acceptable design to allow comparison of the placebo to SRP-only treatment for efficacy because there will not be a spill-over of chlorhexidine to the SRP-only sites, as may be the case for the PerioChip™ group. However, there is no good control for the inactive components of the PerioChip™. Although this is a negligible concern for testing efficacy, since spill-over to the other side of the mouth is not likely to be significant even with chlorhexidine, and there is no reason to suspect that components of the gelatin can exert any therapeutic activity through leaching out, it is more of an issue for safety. Whole-body symptoms (e.g., GI, respiratory, cardiovascular) and pharmacokinetics will not be able to uncover any effect from the inactive components of the placebo, should they exist, because although half of the ***sites*** were not exposed to chip, there is no group of ***subjects*** that was not exposed to either the active PerioChip™ or the placebo chip. Therefore, when comparing for example, a high incidence systemic effect such as upper respiratory tract infection (28.4% PerioChip™ group, 26.1% placebo chip group), it is not possible to rule out the possibility that some inactive component of the PerioChip™ may be contributing. Without a comparison group that was never exposed to the PerioChip™ or placebo chip, this cannot be completely ruled out.

Systemic Effects

For each of the hematological, biochemical and urinary analyses performed, laboratory test results changed less for subjects treated with chlorhexidine chips than those treated with placebo chips. The only instances in which the mean laboratory values were outside the normal laboratory ranges involved placebo-treated patients. There were no clinically significant changes in any laboratory test values. Because pharmacokinetics demonstrated no systemic absorption from PerioChip™, this is not an unexpected finding. Whole-body symptoms as reported by the sponsor demonstrated no systemic adverse events that were reported with greater frequency in the PerioChip™ group as compared to the placebo chip group.

No deaths were reported during the conduct of any of the studies. One subject who withdrew form the study because of pre-existing emphysema, subsequently died. Two subjects withdrew from the pivotal trials due to serious medical events which were not related to the study medication. A total of 15 subjects had serious adverse events, 14 of which were determined to be unrelated to treatment. These events include: emphysema, MI, herniated disks, ankle

surgery, angioplasty, lung masses, excess eyelid soft tissue, car accident, fractured tibia, cardiac bypass surgery, breast reduction, ear problems, and tooth extraction. The subject who reported tooth extraction was enrolled in the one of the European centers and had one tooth which had been treated with PerioChip™ extracted. The subject continued in the study and had other chips placed in other sites without incident.

Local effects

For both pivotal trials, an examination of the oral cavity was performed at each visit after screening and included the following: perioral area/lips, labial mucosa/buccal mucosa, mucolabial fold/mucobuccal fold, gingiva/free and attached, palate/hard and soft, oropharynx/uvula, tongue and floor of mouth. A Chi-square test on the categories listed above indicated that there were no statistically significant treatment differences with regard to the presence of abnormal oral examination findings.

In study No. 89-001, periodontal pocket tissue biopsies were performed on Day 14 and Day 42, on one tooth with a target pocket into which a chip was inserted and one tooth with a target pocket that served as a control site. No statistically significant differences were seen between the chlorhexidine and placebo groups or between treated and untreated sites.

The placement of PerioChip™ as well as the placebo chip caused an initial increase in pain incidence - all of the noted events of swelling and gingival inflammation subsided by the third day. No adverse effects were noted histopathologically on the crevicular or oral epithelium. The only significant adverse event that was observed in the two pivotal trials is "toothache", which according to the sponsor, includes dental, gingival or mouth pain, tenderness, aching, throbbing, soreness, discomfort or sensitivity. The PerioChip™ group reported an incidence of 51%, whereas the placebo chip reported 41% for this adverse event. Generally, the discomfort was mild to moderate in nature. How much of this is associated with the SRP procedure is unknown, since both groups received SRP prior to the chip placement. It should be noted that 70% of the toothaches occurred within the first 3 months of the trials, especially within the first week of the study, strongly suggesting that they were related to the SRP procedure along with chip placement. Although both the placebo and PerioChip™ subjects reported high incidences of toothache, the statistically significant difference supports the notion that the active ingredient also contributed to the discomfort. As a result of the high overall incidence of toothache, and the association with the PerioChip™, the labeling should clearly reflect this potential adverse event.

In terms of "lost chip" as an adverse event, the results of the pivotal trials showed a total of 3 subjects losing the chip the same day it was placed, one subject losing the chip on the second day after placement, one subject the third day, another subject the fourth day, another subject on the fifth day, and another subject on the seventh day. Out of the total number of subjects in both pivotal trials, the incidence of chips lost prior to 7 days is very small. However, one

must keep in mind that the investigators who placed the chips in these trials were highly trained; the average dentist using this product might not possess the same skill and one might expect a higher failure rate when in general use. Based upon the pharmacokinetic and microbiologic data, it is difficult to determine exactly at which point the chip can be considered to have fulfilled its function, and replacement is not necessary. Automatic replacement is not supported by the evidence since an earlier trial demonstrated that placing a second chip one week after placement of the first chip at the same site was actually detrimental to the healing process. Perhaps the most prudent advise would be having the subject receive another chip at the 3 month recall visit if pocket depth is not reduced below 5.0 mm. as was done in the pivotal trials. Based on the evidence submitted, the sponsor should be advised to include a statement in the label advising that in the unlikely event of dislodging of the chip, several actions are recommended. If dislodgment occurs 7 days or more after placement, the dentist should consider the subject to have received a full course of treatment; if dislodgment occurs prior to the second day after placement, a new PerioChip™ should be inserted; and if the dislodgment has occurred between the second and seventh day, the dentist should not replace the chip, but reevaluate the patient at a 3 month recall and insert a new chip if pocket depth has not been reduced below 5.0 mm.

The common local side effects associated with chlorhexidine oral rinses are (1) an increase in staining of teeth and other oral surfaces on certain individuals, (2) an increase in supragingival calculus formation, and (3) an alteration in taste perception. Measurement of SI failed to demonstrate any significant tooth staining, nor was it able to demonstrate increased staining in any of the groups. Although subjects were not specifically queried about taste perception, there was no increased incidence of its reporting in any of the groups. Calculus formation, unfortunately, was not examined in any of the trials. Because accumulation of supragingival calculus is an adverse event associated with use of chlorhexidine rinses, it would have been prudent to have designed the pivotal trials to score calculus with one of the indexes available at the end of the 9 months and make a comparison between the groups. Unfortunately, this was not done, and past discussions with the Agency have not raised this concern. Although all subjects were given SRP at baseline, which would have removed all supra and sub-gingival calculus, no measurements were made during or at the conclusion of the trial which would have determined if calculus formation is related to PerioChip™ placement, as it is related with chlorhexidine rinse usage. Although it is unlikely that significant calculus would develop over the small amount of time that the PerioChip™ is exposed to the oral cavity (7-10 days) compared to the exposure of the chlorhexidine rinse (chronic), nonetheless, the possibility exists. While it would be of interest to answer this question definitively with a trial, the evidence does not warrant requiring the sponsor to conduct another pivotal trial prior to approval. A post-approval, Phase 4 trial could remove the concern about calculus accumulation with use of PerioChip™; however, the decision of the clinical review team is that this is not necessary, given the totality of information.

Labeling

The following pages contains discussion and suggested revision to the sponsor's original version of the label, focusing on the clinical aspects. Following this discussion is the Agency's revised electronic version of the sponsor's proposed label, based upon suggested revisions from each reviewing discipline, discussion during the team labeling meeting, and subsequent deliberation.

*Note: The FDA statistician performed efficacy treatment comparisons on the Intent-to-Treat/Last Observation Carried Froward (ITT/LOCF) population (Refer to statistician's review for further detail.) This differed slightly from the sponsor-performed analyses in that the sponsor did not use the ITT population defined at baseline and then use a LOCF for the remaining visits but instead defined at each monthly visit an ITT population. The results are very similar with either analysis and the conclusions of these trials are identical, regardless of the method of analysis chosen. The numbers that are cited by the sponsor for their efficacy results and are listed in the proposed label as such are those as reported by the sponsor's method.*

As was discussed earlier in this review (See *Choice of Efficacy Variables and relationship to periodontitis*), although PerioChip™ has demonstrated statistically significant reduction of pocket depth which would be useful in a periodontal maintenance program, this outcome alone is not sufficient to claim ' Therefore, in the labeling section

, were changed to

The claim, ' was deleted because the sponsor has not successfully demonstrated reduction of the incidence of as was discussed earlier in this review.

Under the portion of the label, a table is included which lists is included as part of ' Perhaps data should be extracted, and presented separately, even if a small number. The dentist should be instructed concerning appropriate actions (i.e., replacement vs. 3-month recall) dependent upon the day of discussion later in this section) In this table, the most frequently observed adverse event was toothache, also the only adverse event that was significantly higher ($p < 0.05$) in the PerioChip™ group when compared to placebo. Therefore, under the broad heading, Subheading , additional wording was advised to address the transient sensitivity that was reported with use of PerioChip™ as well as the dislodging of the PerioChip™ should it occur. The following wording was suggested:

In the subanalysis of smokers, there was a borderline interaction ($p < 0.10$) between smoking and PPD reduction, with smokers consistently showing less improvement at every time period in both pivotal trials. Because smoking has been shown to be detrimental to the outcome of periodontal therapy, and a large number of the U.S. population are smokers, it may be prudent to reflect in the label that smokers did not achieve satisfactory results from PerioChip™ in the two pivotal trials.

In the section of the label, the sponsor cited the results of their non-pivotal Phase 3 study in Tables 4 and 5, which presented the mean PPD values for the test groups and the number of subjects reporting greater than a 2 mm reduction. Although for dosing and population reasons, this trial was not judged to be pivotal for supporting efficacy, legitimate statements may be made in the label regrading non-pivotal trials as long as they are not false or misleading. One deletion that was made in this section was the statement,

This deletion is required for the same reason as noted earlier in this labeling review - that claim was not demonstrated in both pivotal trials, and therefore should not be discussed in the label in a way that implies efficacy.

Both pivotal trials excluded individuals with diabetes. This was most likely done to prevent confounding in the results, since uncontrolled diabetes is associated with increased periodontal disease. Unless the sponsor plans to conduct another trial which will enroll diabetics, the labeling should reflect this concern. Currently, the label contains a sentence under that states,

It may be advisable to suggest language stating that diabetics were not studied be included in the section of the label as well.

Under the last sentence as submitted by the sponsor states This sentence was revised to The decision about return visits should be left up to the individual practitioner; some dentists may wish to examine the patient for an interim examination to determine if the subject is showing any improvement; their choice may be to pursue a more aggressive treatment if there is no response. In addition, since tooth discomfort is a common adverse event, some dentists may wish to examine patients with this compliant. The sponsor's wording may unnecessarily discourage both of those outcomes.

In terms of instructions to the dentist about replacement of a PerioChip that is prematurely dislodged, it is difficult to determine exactly at which point the chip can be considered to have fulfilled its function, and replacement is not necessary. Automatic replacement is not

supported by the evidence since an earlier trial demonstrated that placing a second chip one week after placement of the first chip at the same site was actually detrimental to the healing process. Perhaps the most prudent advice would be having the subject receive another chip at the 3 month recall visit if pocket depth is not reduced below 5.0 mm. as was done in the pivotal trials. Based on the evidence submitted, the sponsor should be advised to include a statement in the label advising that in the unlikely event of dislodging of the chip, several actions are recommended. If dislodgment occurs 7 days or more after placement, the dentist should consider the subject to have received a full course of treatment; if dislodgment occurs prior to the second day after placement, a new PerioChip™ should be inserted; and if the dislodgment has occurred between the second and seventh day, the dentist should not replace the chip, but reevaluate the patient at a 3 month recall and insert a new chip if pocket depth has not been reduced below 5.0 mm. Wording has been suggested in the proposed label to reflect this opinion. Input from other review disciplines will be helpful to fine-tune the appropriate language.

Redacted 6

pages of trade

secret and/or

confidential

commercial

information

**Recommended Regulatory Action:**

The sponsor has successfully demonstrated the safety and efficacy of PerioChip™. With modifications in labeling, the product may be approved for marketing.

/S/ 11/6/97

Frederick N. Hyman, D.D.S., M.P.H.

cc: Orig NDA
HFD-540/Div File
HFD-540/TL/Kelsey 11/6/97
HFD-540/DO/Hyman
HFD-540/Wilkin
HFD-540/PM/Blatt 11/12/97

**Glossary of Abbreviations**

1. BOP.....Bleeding on Probing
Bleeding on probing is defined as the observed presence of blood after gentle probing to the base of the gingival pocket using a manual North Carolina periodontal probe. A "0" is recorded for no bleeding, and a "1" is used to indicate bleeding. BOP is a cardinal sign of gingival inflammation.

2. GI.....Gingival Index
The Loe Silness Gingival Index is the most popular gingival index in use in clinical trials. GI is scored using a 0-3 scale on or adjacent to six surfaces (mesiobuccal, buccal, distobuccal, mesiolingual, lingual and distolingual) of all natural teeth, excluding third molars, in the upper and lower jaw (a total of 168 possible sites), according to the following criteria:

0 = Absence of inflammation.
1 = Mild inflammation: Slight change in color and texture. No bleeding upon probing.
2 = Moderate inflammation: Moderate glazing, redness, edema, and hypertrophy. There is bleeding upon probing.
3 = Severe inflammation: There is a marked redness and hypertrophy, a tendency to spontaneous bleeding and ulceration.

9 = Missing teeth or unscorable surface.

An average GI score is derived for each subject by summing the individual GI scores of 0-3 and dividing that sum by the number of sites graded for that subject.

3. PAL .....Probing Attachment Level
The distance from a fixed point to the base of the gingival sulcus. This reference point may be a fixed anatomic point on the tooth, such as the cemento-enamel junction, or may be a point created by a custom-formed device which can be replicated accurately. In this trial, PAL was measured after an acrylic stent was placed over the occlusal surfaces of the teeth. The probe tip was guided into the correct location of the sulcus by a mark on the periphery of the stent.

4. PI.....Plaque Index

The Turesky Modification of the Quigley-Hein Plaque Index (PI) examination is the most wisely-used plaque index in clinical trials. Plaque is disclosed using a disclosing solution, Red Cote #28, dispensed immediately prior to the examination. Subjects rinse with 10 ml of Red Cote #28 for 10 seconds, after which subjects will rinse with 15 ml water for 15 seconds. Subsequently, plaque is graded, (maxillary R to L facial L to R palatal,

mandibular R to L facial, L to R lingual). The disclosed plaque is scored using a 0-5 scale on the facial and lingual surfaces of all natural teeth in the upper and lower jaw, excluding third molars. On the facial and lingual surfaces, each tooth receives three scores: ( l ) mesial, (2) middle and (3) distal, for a total of 168 possible sites. Plaque formation is scored using the following criteria:

0 = No plaque present.
1 = Separate flecks of plaque at the cervical margin.
2 = A thin, continuous band of plaque (up to 1 mm) at the cervical margin.
3 = A band of plaque wider than 1 mm but covering less than one-third of the surface.
4 = Plaque covering at least one-third but less than two-thirds of the surface.
5 = Plaque covering more than two-thirds of the surface.
9 = Missing teeth or unscorable surface.

An average plaque score may be derived for each subject by summing the individual plaque scores (six per tooth of score 0-5) and dividing that sum by the number of sites graded for that subject.

5. PPD.....Probing Pocket Depth
The distance from the coronal edge of the gingival margin to the base of the gingival sulcus, as measured by a periodontal probe.

6. SI.....Staining Index
The following Staining Index was used in this clinical trial:

0 = No observable stains of supragingival tooth surface.
1 = Slight staining of supragingival tooth surface.
2 = Moderate staining of supragingival tooth surface.
3 = Severe staining of supragingival tooth surface.

7. SRP.....Scaling and Root Planing
Scaling is "Instrumentation of the crown and root surfaces of the teeth to remove plaque, calculus, and stains from these surfaces." Root planing is "a definitive treatment procedure designed to remove cementum or surface dentin that is rough, impregnated with calculus, or contaminated with toxins or microorganisms."

Blay
HFD-540

DEC 20 1997

# Dental Officer's Review of NDA 20-774
Safety Update

| | | | |
|---|---|---|---|
| **Drug:** | PerioChip ™ (2.5 mg. chlorhexidine gluconate bound in a hydrolyzed gelatin matrix) | **Serial Number:** | 000 |
| | | **Submission date:** | November 18, 1997 |
| | | **Received date:** | November 21, 1997 |
| **Sponsor:** | Perio Products, Ltd. | **Review date:** | November 25, 1997 |
| | | **PDUFA date:** | **December 20, 1997** |
| **Pharmacologic Category:** | Anti-microbial | **Project Manager:** | Roy Blay |
| **Proposed indication:** | Adjunct to scaling and root planing procedures for the treatment of periodontitis. | **Reviewer:** | Fred Hyman |

**Introduction:**

The original submission to this NDA was made on December 20, 1996. As of the date of this review, each discipline's review has been completed and an "approvable" letter is awaiting final signature of the Division Director. On November 18, 1997, the 120 Day Safety Update Report was submitted to the Agency for review. This review contains adverse events received by Perio Products during the period October 1, 1996 through October 31, 1997. Although the sponsor has submitted a very up-to-date report that includes more than the mandatory 120 days of safety data, it would have been preferable for the Agency to have received safety data that covered a time period that ended earlier and was submitted earlier in the review process.

**Discussion:**

This 120 Day Safety Update Report contains reports of all adverse events that have occurred during clinical trials, as well as those that have been described through postmarketing experience in countries where the drug has been approved for marketing.

*Ongoing Clinical Trials*

All serious adverse events and discontinuations due to adverse events from the clinical studies with PerioChip have been included in this submission. Copies of case report forms for patients who died or discontinued the study due to adverse events were also included. Study 95-401 is a 2-year, long-term maintenance study trial that began in 1996. It is

being conducted in Israel, not under an IND. Study 96 PC-01, is a 12-month pharmacoeconomic trial being conducted under IND in 10 academic centers across the United States.

Three serious adverse events were reported during study 95-401, one of which was related to the PerioChip - an allergy to chlorhexidine. The subject was removed from the study medication and recovered uneventfully. To date, during the conduct of 96 PC-01, a total of 9 serious adverse events have been reported, none of which are related to the study medication. The most serious adverse event was death from a motor vehicle accident.

*Postmarketing Surveillance*

A summary of postmarketing adverse events from Israel and the United Kingdom, the two countries where the PerioChip has been approved for marketing and is currently commercially available, is also included in this submission. At the time of the initial submission of this NDA, PerioChip had already been marketed in Israel, and a summary of adverse events was included in the NDA. Since that time, no additional reports of adverse events have been received by the sponsor from users of the product in Israel. In the United Kingdom, the product was introduced in January, 1997, shortly after the submission of this NDA. Since that time, adverse events were reported for twelve patients in the U.K., none of which were serious. The events were very similar to those reported in the pivotal trials for this NDA, and none were events that would warrant a change in the currently proposed labeling for the NDA. Of note is that two of the reports involve premature expulsion of the chips from the pocket (one report notes a patient with 2 chips in succession that were expelled prematurely, the other notes 3 chip replacements with each being prematurely expelled). During the labeling review of this NDA, it was decided to place wording in the label to advise practitioners of the possibility for expulsion of the PerioChip and appropriate action to implement. Although the sponsor recorded the incidence of expelled chips as less than 1% in the original NDA submission, it was noted that this rate was among a group of clinicians who were highly trained to place the PerioChip as a part of a clinical trial. It was predicted that the incidence of expelled chips would be higher during general use. Although far too few numbers of reports have been provided to reach any conclusions, the receipt of 2 practitioner's reports of multiple chip expulsion out of the total of 12 reports received may support this concern.

**Recommended Regulatory Action:**

This Safety Update does not provide evidence that would negatively impact on the approvability of this product.

/S/

Frederick N. Hyman, D.D.S., M.P.H.

cc: Orig NDA
HFD-540/Div File
HFD-540/DD/Wilkin
HFD-540/TL/Kelsey
HFD-540/DO/Hyman/Gilkes
HFD-540/PM/Blay
HFD-540/See
HFD-725/Srinivasan
HFD-830/Vidra

12/1/97

12/20/97 Note: The reviewer states that as of the date of (his) review, each discipline's review has been completed and an "approvable" letter is awaiting final signature of the Division Director. In fact, the date of his review was November 25, 1997, which was the same day the Division Director signed the approvable letter.

APR 10 1998

# Dental Officer's Review of NDA 20-774
Labeling Amendment

| | | | |
|---|---|---|---|
| **Drug:** | PerioChip® (2.5 mg. chlorhexidine gluconate bound in a hydrolyzed gelatin matrix) | **Serial Number:** | BL |
| | | **Submission date:** | December 9, 1997 |
| | | **Received date:** | December 11, 1997 |
| **Sponsor:** | Perio Products, Ltd. | **Review date:** | March 27, 1998 |
| | | **PDUFA date:** | May 9, 1998 |
| **Pharmacologic Category:** | Anti-microbial | **Project Manager:** | Roy Blay |
| **Proposed indication:** | Adjunct to scaling and root planing procedures for the treatment of periodontitis. | **Reviewer:** | Fred Hyman |

**Background**

On November 25, 1997, the Agency issued an approvable letter to PerioProducts, Ltd, the sponsor of PerioChip®, a gelatin chip containing 2.5 mg chlorhexidine gluconate, for the indication, "adjunct to scaling and root planing procedures for reduction of pocket depth in patients with adult periodontitis". The approval is contingent upon acceptable response to CMC concerns. The sponsor's label that was submitted with the original NDA was revised and sent to the sponsor along with the approvable letter. In this current submission, the sponsor has proposed certain changes to the FDA label. This review will address the acceptability of each of these revisions.

The following section of this review contains each proposed change and a discussion of the acceptability of the change. Following this section are two labels. The first is the label that accompanied the approvable letter, with strikeout denoting the sponsor's requested deletions and redline denoting the sponsor's requested additions. The second label is the final approved label to accompany the approval letter.

**Proposed Changes:**

*Revision #1:*

After the third sentence of the Pharmokinetics subsection of the section, the following sentence has been added:

*Sponsor's Rationale for Revision #1:*

The sponsor believes that this sentence provides additional information to clinicians, demonstrating that *in vivo* data supplements the *in vitro* data.

*Reviewer's Comment:*

After discussion with the biopharmaceutics reviewer assigned to this NDA, the decision was made that the statement does not add useful or accurate information. is not sufficiently accurate to provide useful information, the maintenance of the 50 µg/mL levels was not discussed, and the variance associated with the 50 µg/mL level was not provided. This statement will not be appear in the approved label.

*Revision #2*

The sixth sentence of the Pharmacokinetics subsection (line 43) of the section has been revised as follows:

from:

to:

*Sponsor's Rationale for Revision #2:*

The sponsor feels that the variation may be due to more than just the actual chlorhexidine release, i.e., other sources of variability may include the minute amount of subgingival fluid and sampling technique.

*Reviewer's Discussion:*

The biopharmaceutics reviewer disagreed with the inclusion of the phrase as it changes the meaning of the sentence to imply that the analytical method was somehow inadequate or not of sufficient rigor to provide proper data. The reviewer does not believe that the analytical variability is a major component in the observed variance. The original statement will appear in the approval label.

*Revision #3:*

The sponsor has revised the third and fourth sentences of the second paragraph of the subsection of the section as follows:

from:

to

Concomitantly,

Under the sponsor wishes to delete the following sentence:

*Sponsor's Rationale for Revision #3:*

The sponsor believes that the significant effect on BOP in Study 94-002 should be noted. Regarding the smoking status effect on PPD reduction, the sponsor believes that although the effect on PPD was smaller in smokers than in nonsmokers, it was in the same direction. Furthermore, the sponsor believes that the notation of the plaque and gingivitis outcomes should be included under the subsection of the section, rather than section.

*Reviewer's Discussion:*

*Attachment Level*

Prior to addressing this proposed revision, the use of the sentence,

in this section requires some discussion, in light of some new policies regarding primary endpoints that have been formulated in the Division since the original NDA review. In the pivotal trial protocols, the sponsor had stated that the primary efficacy variables in this study were 1) reduction from baseline of PPD and 2) the stabilization of PAL. The sponsor was aware that a "win" required demonstration of both of these outcomes for both pivotal trials. The sponsor's definition of "stabilization of PAL" is that the loss of attachment in the PerioChip™ group was not to exceed 20% of the loss of attachment in the placebo (i.e., if the placebo group lost a mean of 1.0 mm of attachment, the PerioChip™ group must have lost no more than 1.2 mm to win). It has not been demonstrated that there is any difference between the PAL reduction with PerioChip™ + SRP vs. SRP alone; furthermore, all 3 groups demonstrated a gain in PAL. It was determined that this is sufficient to claim that the PAL hadn't worsened during the 9 months of the trial (Refer to the original NDA review for a full discussion).

Were the discussion of the primary efficacy variables to have occurred in this Division at the present time, rather than in HFD-160 several years ago, the sponsor would probably have been encouraged to consider maintenance of PAL as a tertiary endpoint, or even as a measure of safety, rather than a primary outcome variable. Nonetheless, because the sponsor set up both variables are requirements for a "win" and achieved the goal, their statement regarding maintenance of probing attachment level in the Clinical Studies section of the label is permissible. All references to treatment of periodontitis were removed in the original labeling review to clarify that the "maintenance of PAL" does not imply treatment of periodontitis.

*Bleeding On Probing*

*Note: The following information was presented in full detail in the original NDA review. It is summarized here.*

Three phase 3 trials were submitted to the original NDA in support of the safety and efficacy of PerioChip - #92-002, 94-002, and 94-003. Trial #92-002 was, by the sponsor's own admission, not considered to be pivotal for several reasons, including the use of the controversial split-mouth design, lack of placebo group, and short duration. The other two Phase 3 trials, #94-002, and 94-003, were both parallel, randomized, double-blinded, placebo-controlled trials, each conducted in five U.S. centers. Both of these trials met the Agency criteria of well-controlled clinical trials. In order for the sponsor to have won on BOP, a secondary outcome variable, the pivotal trial results must support the drug's efficacy.

In study 94-002, the difference between the number of sites that had BOP in the

PerioChip™ group demonstrated statistical significance when compared to the number of sites with BOP in the placebo chip group as well as when compared to SRP alone. This was a consistent result, achieved at all time points examined during the trial. In study 94-003, on the other hand, no statistically significant difference was demonstrated between the PerioChip™ group and either the placebo group or SRP alone. When study 94-003 was examined by observation period, a further analysis of the results provided the following information: Week 6 of the 9-month trial was the only time point in which subjects who received PerioChip™ experienced fewer bleeding episodes compared to both control groups; however, this result did not reach statistical significance. At Month 6, the PerioChip™ plus SRP group experienced significantly more bleeding episodes compared to the SRP alone group ($p = 0.062$). **Given the equivocal nature of these results, the claim that PerioChip™ reduces bleeding on probing is not supported.** It would be misleading to state that trial 94-002 demonstrated BOP without balancing that statement with the information that 94-003 did not demonstrate this effect. The inclusion of both of these statements consecutively may be a viable solution, but a more appropriate and truthful statement is that the results of the trials demonstrated equivocal findings, or better,

Both plaque indexes and gingival indexes were measured in the trials as secondary endpoints and in both trials, demonstrated insignificant changes with no particular observable trend. Whereas the BOP endpoint was demonstrated in one pivotal trial, but not supported with the other, the changes in plaque and gingivitis were consistently one of in both trials. Therefore, stating that the effects of BOP reflects an uncertainty about the results, whereas reflects the consistency of results with the plaque and gingivitis outcomes. The sponsor's proposed statement, is therefore accurate and acceptable.

The original intent of including the statement regarding lack of effect of PerioChip on gingivitis, plaque development and bleeding upon probing in the Indications and Usage section was to prevent misunderstanding among practitioners - because the PerioChip reduces pocket depths, it may also be assumed by dentist that it will also reduce other common parameters of periodontal disease, such as BOP, gingivitis, and plaque development. However, after consideration of the purpose of the Indications and Usage section, the statement appears to be more appropriately located in the Clinical trials section.

*Smoking*

The sponsor's proposed statement,

does not supply the reader of the label with a factual understanding of smoking's effect on PPD reduction in these trials. As proposed, the above wording does not provide the outcome in smokers which is as follows:

However, in all fairness to the sponsor, the studies were not powered to find a significant difference in that subgroup - were the sample size increased sufficiently, it is likely that a significant difference might be demonstrated, although based on the original analysis, the magnitude would be much less in smokers than non-smokers. Although the magnitude may not be the same, it is not a requirement that adjunctive claims to SRP demonstrate a minimum magnitude in order to gain an efficacy claim. In addition, the sponsor is correct in stating that the trend of improvement in smokers with PerioChip is observed. The salient point to convey, however, is that there is a significant interaction between smoking and PPD (sponsor's p-value 0.073; FDA statistician's p-value 0.0498 - interaction p-values are considered significant at values of up to 0.10 - 0.15). The data as reported in the original NDA submission with respect to smoking are as follows:

This finding is consistent with the consensus of information regarding smoking and periodontal disease. For example, a meta-analysis of data examining the effect of smoking on loss of periodontal tissue support demonstrated an overall increased risk for severe periodontal disease (Odds Ratio of 2.82, 95% Confidence Interval 2.36 to 3.39).[1] In an attempt to quantify the effects of smoking, Haber et al suggested that the excess prevalence of periodontal disease in the population attributed solely to smoking is by far greater than the one owed to other systemic predispositions, such as diabetes mellitus.[2]

As a suggestion to convey the message that the therapeutic effect of the PerioChip is negatively affected by smoking, but not to stigmatize PerioChip because they were one

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[1]Papapanou P, Periodontal Diseases: Epidemiology, Ann Periodontol 1996:1:1-36.

[2]Ibid

of the first sponsors to specifically examine this outcome, the following wording is proposed:

Therefore, the acceptable labeling will state in the Clinical Studies section:

Concomitantly, the statement concerning the lack will be removed from the section.

*Revision #4:*

The term has been removed from information concerning has been placed in the first sentence of the third paragraph of the section (line 157) as follows:

from

to

*Rationale for Revision #4:*

The sponsor believes that the loss of a PerioChip is not a safety concern, but rather an efficacy concern. In the pivotal trials, the was not evaluated as a separate item. Therefore, the number of was moved to the section.

*Reviewer's Discussion:*

After considering the sponsor's rationale, it seems reasonable that the _ is not a safety concern, and as such, does not belong in the section. The reason it was placed in the revised label was because the sponsor's adverse events data in the original NDA submission included as a part of the general adverse event. The sponsor's suggestion that the number of chips lost during the pivotal trials be reported in the section of that discusses replacement of a prematurely dislodged PerioChip is a good one. Also as a result of removing the " from the adverse event, the number of subjects and associated percent in the section decreased. To maintain a listing of adverse events in the proper decreasing order, the order of the adverse event and adverse event has been switched.

*Revision #5:*

The sponsor has proposed the addition of the term to the fifth sentence of the section and in the title of Table 3, as shown below:

from:

to:

Concomitantly, the title of Table 3 has been updated to reflect this change

from:

to:

*Rationale for Revision #5:*

The sponsor feels that the term should be added as a descriptor for Table 3. PerioProducts, Ltd points out that there were additional adverse events that occurred with a frequency of ≥ 1% which are not included in the table. They believe that listing only clinically relevant adverse events will be a convenience to the dentist.

*Discussion:*

The sponsor is correct in stating that the adverse events noted in Table 3 is not a complete list. In the original NDA review, the table of all adverse events, categorized by body system, was presented and discussed. Due to the lack of association of the PerioChip with any systemic effects, the sponsor reduced the table to what they believed were clinically relevant adverse events such as toothache and gum hyperplasia, which may be expected from the combination of SRP with the placement of the chip. During the Division's review of the label, some discussion ensued about the use of the ' as a descriptor to Our decision at the time was to drop because this is not an acceptable way to report adverse events in a label. Although determinations can be sometimes be made about the clinical relevance of certain adverse events from the pivotal clinical studies, weaker associations may not be detectible until much post-marketing data is collected. Therefore, the determination of clinically relevant can not be made conclusively at this time, and should not appear on the label in this manner.

will remain as the title of the table. In addition, the final label will contain all of the adverse events that appear with a frequency of ≥ 1%. During the approvable letter that went out to the sponsor, the list was not complete. The revised table, containing all of the reported adverse events occurring with a frequency ≥ 1% from the pivotal trials, is as follows: (see top of next page)

**Table 3**
**Adverse events (frequency ≥1% for the PerioChip group)**
**reported from 2 five-center U.S. clinical trials**

| | PerioChip Total N=225 | | Placebo Chip Total N=222 | |
|---|---|---|---|---|
| | N | % | N | % |
| All Patients with Adverse Events | 193 | 85.8 | 189 | 85.1 |
| Toothache* | 114 | 50.7 | 92 | 41.4 |
| Upper resp tract infection | 64 | 28.4 | 58 | 26.1 |
| Headache | 61 | 27.1 | 61 | 27.5 |
| Sinusitis | 31 | 13.8 | 29 | 13.1 |
| Influenza-like symptoms | 17 | 7.6 | 21 | 9.5 |
| Back pain | 15 | 6.7 | 25 | 11.3 |
| Tooth disorder** | 14 | 6.2 | 15 | 6.8 |
| Bronchitis | 14 | 6.2 | 7 | 3.2 |
| Abscess | 13 | 5.8 | 13 | 5.9 |
| Pain | 11 | 4.9 | 11 | 5.0 |
| Allergy | 9 | 4.0 | 13 | 5.9 |
| Myalgia | 9 | 4.0 | 9 | 4.1 |
| Gum hyperplasia | 8 | 3.6 | 5 | 2.3 |
| Pharyngitis | 8 | 3.6 | 5 | 2.3 |
| Arthralgia | 7 | 3.1 | 13 | 5.9 |
| Dysmenorrhea | 7 | 3.1 | 13 | 5.9 |
| Dyspepsia | 7 | 3.1 | 6 | 2.7 |
| Rhinitis | 6 | 2.7 | 11 | 5.0 |
| Coughing | 6 | 2.7 | 7 | 3.2 |
| Arthrosis | 6 | 2.7 | 4 | 1.8 |
| Hypertension | 5 | 2.2 | 6 | 2.7 |
| Stomatitis ulcerative | 5 | 2.2 | 1 | 0.5 |
| Tendinitis | 5 | 2.2 | 1 | 0.5 |

* Includes dental, gingival or mouth pain, tenderness, aching, throbbing, soreness, discomfort or sensitivity
** Includes broken, cracked or fractured teeth, mobile teeth, and lost bridges, crowns, or fillings

*Revision #6:*

The following sentence has been inserted after the first sentence in the first paragraph of the section:

*Rationale for Revision #6:*

The sponsor feels that this sentence should be added based upon the comment from the bipharmaceutics reviewer in the approvable letter.

*Discussion:*

The addition of this sentence is informative and truthful and will be allowed.

**Proposed Minor Changes:**

The following list contains minor changes, which include rounding of numbers, font size, order of items, and trademark identification as follows:

1. The symbol has been replaced by throughout all labeling, due to a change in the status of the trademark of the product name.

2. In the third sentence of the second paragraph of the subsection of the section, the mean value for the second peak at 72 hours, has been rounded off to for consistency with all other PK values int hat paragraph.

3. The font size of the paragraph following Table 2 has been increased to match the font size of the surrounding text. It appeared as though this text was a footnote to Table 2, which would not be appropriate, since this statement applies to the entire subsection.

4. In Table 3 (Adverse Reactions), the term and all corresponding data has been moved, from below the term to above the term Since lost chips were removed from the term , the frequency of this term is now lower than the frequency of therefore, the term has been moved so that the terms are arranged in decreasing order of frequency.

*Discussion:*

All of the proposed minor changes are acceptable.

**FDA-Initiated Change:**

After a review by the Office Director of the Office for Drug Evaluation 5, which includes the

Division of Dermatologic and Dental Drug Products, a concern was raised about the use of the abbreviation PPD for "periodontal probing depth." Since PPD is more widely accepted in the medical community as an abbreviation for Purified Protein Derivative, it is recommended that "PPD" not be used in the label. The Proceedings of the 1996 World Workshop in Periodontics (Annals of Periodontology, Volume 1, Number 1, November 1996) used the abbreviation "PD" consistently to refer to "probing depth" . There is no difference between "probing depth" and "probing pocket depth" when used in the periodontal context. It is therefore recommended that "PD" be substituted for the abbreviation "PPD" where it occurs in the label.

The following pages contain the label that accompanied the approvable letter, with strikeout denoting the sponsor's requested deletions and redline denoting the sponsor's requested additions.

APPEARS THIS WAY
ON ORIGINAL

Redacted 6

pages of trade

secret and/or

confidential

commercial

information

The following pages contain the new approved label.

Redacted 6

pages of trade

secret and/or

confidential

commercial

information

**Recommended Regulatory Action:**

The approval of PerioChip is contingent upon resolution of Chemistry deficiencies. The final approved label is provided in the prior six pages of this review.

/S/ 3/27/98

Frederick N. Hyman, D.D.S., M.P.H.

cc: Orig NDA
HFD-540/Div File
HFD-540/DD/Wilkin
HFD-540/TL/Kelsey 3/20/98
HFD-540/DO/Hyman
HFD-540/PM/Blay
HFD-540/See 4/10/98
HFD-725/Srinivasan
HFD-830/Vidra