1. General Information

Device Generic Name:	Endosseous Implant for Bone Filling and/or Augmentation
Device Trade Name:	PepGen P-15™ (formerly known as OsteoGraf CS-300)
Applicants Name and Address:	CeraMed Dental, L.L.C. 12860 W. Cedar Drive, Suite 110 Lakewood, CO 80228
Premarket Approval (PMA) Number:	P990033
Date of Panel Recommendation:	January 12, 1998
Date of Notice of Approval to the Applicant:	OCT 25 1999

2. Indications for Use

PepGen P-15 particles are intended for use in the treatment of intrabony periodontal osseous defects due to moderate or severe periodontitis.

3. Contraindications – None known.

4. Warnings – (See device labeling).

5. Precautions – (See device labeling).

6. Adverse Effects of the Device on Health

No instances of any tissue reaction, inflammation, particle migration, or other local reactions related to the PepGen P-15 were observed during two multicenter clinical trials (65 patients).

The following complications have been reported in literature with regard to surgical bone grafting procedures in general: implant migration, particle extrusion, wound dehiscence, loss of vestibular depth, sterile abscess, infection, and varying levels of mental nerve anesthesia including permanent paresthesia or anesthesia.

7. Device Description

PepGen P-15 consists of the following two components:

- Anorganic bovine derived hydroxylapatite particles, 250-420 μm in diameter with a mean diameter ≅ 300; and
- P-15, a synthetic replication of a peptide sequence of the α chain of Type I collagen.

Physical and handling characteristics of PepGen P-15 are identical to those of its anorganic bovine derived hydroxylapatite matrix. The addition of the P-15 synthetic peptide to the

anorganic bovine derived hydroxylapatite matrix serves to enhance performance characteristics by accelerating cell binding, thereby enhancing bone ingrowth into the defect site (see Summary of Preclinical Studies).

Mechanism of Action:

Hydroxylapatite is the primary mineral component of teeth and bones. It has been shown to be an effective bone filling material, acting as biocompatible scaffolding for osteoconduction in defect sites.

PepGen P-15 was developed by combining hydroxylapatite made from anorganic bovine bone with a synthetic peptide having a small linear chain of 15-amino acid residues. This amino acid sequence is a synthetic replication of the sequence contained in residues 766-780 of the α chain of Type I collagen, which contains a putative cell binding site. It is also believed that this region of Type I collagen does not contain immunologically active sites. P-15 is adsorbed to this hydroxyapatite to form PepGen P-15. *In vitro* studies (see Summary of Preclinical Studies) have demonstrated that the attachment of fibroblasts to hydroxyapatite particles is enhanced when P-15 is present on the particles. In addition to improved cellular attachment, the lack of putative antigenic sites is believed to either eliminate or greatly reduce both immediate and delayed immune responses that may be associated with allografts such as freeze-dried bone allografts and xenografts.

8. Alternative Practices and Procedures

Alternative treatments include the use of other bone filling materials such as autogenous intraoral bone grafts, autogenous hip marrow grafts, freeze-dried and decalcified freeze-dried bone allografts, hydroxylapatite, calcium phosphate materials, bioglasses, coral, and polymeric synthetic bone replacement materials. In narrow three wall defects no grafting material may be required at all. In addition, guided tissue regeneration (GTR) procedures without the use of any grafting material has been advocated. The present benchmark against which other non-autogenous bone filling materials are compared is decalcified freeze-dried bone allograft.

9. Marketing History

PepGen P- 15 has been marketed in the European Communities since March 1999 after undergoing the CE-Mark certification process and being issued an EC Design Examination Certificate (CE 01972) by the British Standards Institute.

PepGen P-I 5 has been marketed in Canada since March 1999 via a Part V submission (#11688) and issuance of a Notice of Compliance by the Canadian Health

Protection Branch. The Canadian Notice of Compliance was originally issued in August 1997 and marketing of PepGen P-15 began in March 1999.

10. Summary of Preclinical Studies

Biocompatability

Tripartite biocompatibility testing (ISO 10993-1) has been performed on PepGen P-15.

The following tests were performed:

- In Vitro Hemolysis, Saline Extract – A sodium chloride extract was added to tubes of whole rabbit blood. The mean hemolysis value was 0%.
- in Vitro Cytotoxicity, MEM Elution – An extract of OsteoGraf CS-300 (PepGen P-15) was made using minimal essential medium, and flowed over a confluent monolayer of mouse fibroblasts. No evidence of cell lysis or cell toxicity was noted.
- Ames Mutagenicity, Saline Extract – Reversion of Ames Salmonella typhimurium bacterial in histidine deficient medium containing a saline extract from the device, to wild types, were compared to reversions in non-device extract controls. The saline extracts did not cause mutagenicity changes in these bacteria.
- Systemic Toxicity in Mice, Saline and Cottonseed Oil Extracts – saline and cottonseed extracts from the device were injected intravenously or intraperitoneally in rats. As compared to vehicle alone controls, there was no mortality or evidence of significant systemic toxicity from the extracts.
- Intracutaneous Toxicity in Rabbits, Saline and Cottonseed Oil Extracts – saline and cottonseed extracts from the device were compared to blank vehicles, for erythema and edema in the rabbit. There was no evidence of significant irritation or toxicity from the extracts.
- Delayed Contact Sensitization in the Guinea Pig, Saline and Cottonseed Oil Extracts – Saline and cotton seed oil extracts form the device were individually injected intradermally into guinea pigs and occlusively patched. Following a recovery period, a challenge patch was placed. Sites were evaluated at 24 to 96 hours. Neither extract demonstrated contact sensitization.
- Muscle Implantation in Rabbits, 30-Days – the device was surgically implanted in the muscle of the rabbit. At 30 days, there was no significant difference between the device and the negative control. Microscopically, the device was classified as a moderate irritant, as compared to the reference control.

The results of this series of biocompatibility tests show PepGen P-I 5 to be nonsensitizing, nontoxic, nonhemolytic, and nonmutagenic. These tests also indicated that it was a mild to moderate tissue irritant in the rabbit. However, clinical reports characterize PepGen P-15 as nonirritating to human oral tissues.

Published In-Vitro Studies

The following (references #1 – 7) are the basis for claims of cellular attraction and attachment, as well as a basis for subsequent animal and clinical studies. *(Note: "ABM" refers to Anorganic Bovine Mineral, or Anorganic Bovine Derived Hydroxylapatite. This is the same as OsteoGraf N-300).*

(1.) Qian et.al compared attachment of human dermal fibroblasts on 1) ABM/P-15 and 2) ABM particles. Radiolabeled fibroblasts were used to determine quantity of cells adherent to the study materials, and to evaluate the synthesis of both, DNA and proteins. Cultures were also stained to measure alkaline phosphatase. ABM/P-I5 fibroblasts formed monolayers, and stained heavily for alkaline phosphatase, suggesting the presence of osteoblast-like cells. The uncoated ABM cells did not stain at all. Compared to uncoated ABM particles, ABM/P- 15 particles demonstrated enhanced viable fibroblast cell, binding.

(2.) Bhatnagar et.al studied fibroblast binding to HA particles containing P-15. P-I 5 was added to dishes of human fibroblasts. The resulting cell activity was observed to compare the binding of fibroblasts to P-15 versus collagen. P-15 had a marked inhibitory effect on cell binding to collagen, indicating significantly greater cell binding to P-15, as compared to collagen.

(3.) Sadeghi et.al evaluated the response of periodontal ligament fibroblasts to P-15. PDLF cells were added to ABM and ABM/P-15 particles in siliconized culture tubes to examine the attachment of periodontal ligament (PDL.F) fibroblasts on ABM/P- 15. ^{3}H-thymidine and ^{4}C-proline to monitor DNA and protein synthesis respectively. Significantly more cells attached to ABM/P-15 particles compared to uncoated ABM particles. Cells proliferated on ABM/P-15 and were more active in protein synthesis.

(4.) Sadeghi compared attachment and proliferation of periodontal ligament cells on ABM/P-15 versus plain ABM. Periodontal ligament cell cultures were incubated on ABM/P-15 particles of different P15 concentrations. P- 15 concentration was assayed by fluorimetry. Incorporation of radiolabeled thymidine and proline was measured with a scintillation counter in order to compare the number of cells attached and their viability. ABM/P-is cells attached in greater numbers and proliferated more readily than ABM cells.

(5.) Bhatnagar evaluated migration patterns of fibroblasts. ABM and ABM/P-15 particles were placed in agarose gel to examine the potential of P-15 to promote cell migration. ABM/P-15 cultures markedly stimulated the migration and attachment of cells compared microscopically with the ABM cultures.

(6.) Qian et.al evaluated the alkaline phosphatase activity of neonatal human dermal fibroblasts. Fibroblasts were cultured with either ABM or ABM/P-15 to evaluate alkaline phosphatase activity as measured by the behavior of neonatal human dermal fibroblasts. ABM/P-15 cells formed three-dimensional colonies; ABM cells formed only monolayers. A BM/P-15 showed the presence of significant amounts of alkaline phosphatase.

(7.) Moses et.al evaluated periodontal ligament cell spreading, by scanning electron microscopy, on various bone grafting materials, human periodontal ligament fibroblasts (PDLF) were grown on a variety of bone replacement graft materials, including ABM/P- 15 peptide. At 4 hours *in vitro,* cells spread more rapidly on the ABM/P-l 5 than on other synthetic and natural hydroxylapatites, polymers, coral, and glasses. The cell spreading rate was as rapid on the ABM/P-15 as on demineralized and non-demineralized bone. Cells were flattened and well spread out on the ABM/P-l 5 particles.

In-Vivo Study

The study in reference #8 is the basis for a claim of improved bone growth and the basis for subsequent clinical studies.

Parsons et.al evaluated the efficacy of ABM/P-I5 as a bone graft material in delayed healing rabbit bone defects. ABM/P-15 or ABM was placed in contralateral skull defects of ten New Zealand white rabbits. Quantitative image analysis indicated that no fibrous tissue encapsulation occurred in any of the implant sites. ABM/P-I5 sites exhibited significantly more linear bone ingrowth than the ABM sites.

Note: The above tests were exempt from GLP because they were basic exploratory studies conducted to determine whether the device might have potential utility.

10. Gender Analysis

The investigators in this study neither made note of any gender related differences in periodontal disease severity, nor observed any preferential response in its treatment. The dental literature contains no studies indicating that adult type periodontitis has a greater predilection for one gender over the other. There is also no evidence in the literature that indicates a differential response to periodontal treatments of any kind. Therefore, this study reflects the general population with respect to gender related study selection, gender related disease severity, and gender related treatment response.

11. Summary of Clinical Studies

There are two multicenter clinical studies presented in this Premarket Approval Application. Both studies were prospective, double blind, and performed by calibrated measurers. A same mouth design was used. Each patient supplied both experimental and control sites. Patients selected for both studies were randomly selected with respect to gender and treatment.

Clinical *Study #1*

The first clinical study compared PepGen P-15 to benchmark surgical and grafting treatment modalities. The study objective was to show that the test material was at least as safe and effective as DFDBA. The primary clinical outcome goal was at least 1 mm difference between experimental and control measurements at 6 months, in clinical probing attachment gain,

probing depth decrease, and percent defect fill. Percent defect fill and decrease in probing depth were secondary goals. Thirty one patients (16 males and 15 females) with a mean age of 51.5 and age range of 37 to 76, were treated. Each patient in the study supplied three eligible periodontal defects, and acted as a negative control, a positive control, as well as an experimental treatment arm. For each patient, after surgical debridement, one site received no bone filling material (negative control site), one site received demineralized freeze-dried bone allograft (positive control site), and the third site received OsteoGraf CS-300, (experimental site). Patients were seen for a reentry surgical appointment at 6 months where measurements were made. The patients were also seen at 12 months for clinical measurements, and to evaluate healing. Study results demonstrated statistically significant superiority of the test material, OsteoGraf/CS-300, over both debridement and DFDBA for percent defect fill in the vast majority of sites. All criteria for success of the test material set forth prior to initiation of the study were met: i.e., OsteoGraf/CS-300 was equivalent to or better than DFDBA in attachment gain, percent defect fill, and decrease in probing pocket depth. OsteoGraf CS-300 performed better than debridement in those same measures.

Table I – Clinical Study #1 Results
Defect Results

6-7 month reentry

	PepGen P-15 (a) N=31	DFDBA (b) N=31	DEBR (c) N=31	P*
Original Defect	3.6 mm	4.0 mm	3.8 mm	
Residual Defect	0.7 mm	1.5 mm	1.3 mm	a/b, a/c
Amount Defect Fill	2.8 mm	2.0 mm	1.5 mm	a/b, a/c
% Defect Fill	72.3%	51.5%	40.3%	a/b, a/c
Crestal resorption	0.1 mm	0.5 mm	1.0 mm	a/c, b/c
%Defect Resolved	79.9%	64.6%	66.0%	a/b, a/c

(a) PepGen P-15 (formerly known as OsteoGraf CS-300)
(b) DFDBA = decalcified freeze-dried bone allograft.
(c) DEBR = defect debridement (no graft material).
P* indicates that when comparing data in column a compared to data in column b, data in column b compared to column c, or data in column a compared to column c, a Parametric one way ANOVA with Student Neuman-Keuls and nonparametric Kruskall-Wallis ANOVA by Ranks with Dunn's post-test used for analysis, indicated statistical significance.

Table I table compares treatment with PepGen P-15 to the benchmark grafting material, decalcified freeze-dried bone allograft. Results indicate that the addition of PepGen P-15 to

periodontal defects resulted in a statistically greater amount of bone fill and greater percent bony defect fill than defect debridement alone, or decalcified freeze-dried bone allograft. Percent defect fill is considered by many clinicians to be a measure of treatment success. This may be compared to historical data in Table II, below. This data was obtained from studies published in the reviewed literature.

Table II - Historical Overview of Controlled Intra-Patient Reentry Studies

	Studies (#)	# of Pts. (Mean)	% Defect Fill	CPAL (Gain)	Prob. Depth (Decrease)
DFDBA	13	10.6	56%	1.8mm	2.9 mm
DEBR	15	15.6	26%	1.2 mm	2.7 mm
HA	10	14.4	50%	1.5 mm	2.5 mm

DFDBA = decalcified freeze-dried bone (graft material)
DEBR = defect debridement (no graft material)
HA = hydroxyapatite (graft material)
CPAL = coronal probing attachment level (increase in probing attachment level)
Prob. Depth = decrease in clinical probing attachment level

Probing attachment level reflects the amount of alveolar bone lost due to periodontal disease, and conversely, the amount of bone left to anchor and support a tooth. It is measured by subtracting gingival recession measurements from probing pocket depths. Table II reviews data from 38 clinical studies, and indicates that, from a historical perspective, periodontal defects demonstrated approximately 50% or greater defect fill. A defect fill of 50% or greater, has been a historical benchmark for treatment success. Table III, below, displays the percentages of cases where defect fill was ≥90%, ≥50%,<50%, and <20% respectively.

Table III – Results of Clinical Study #1
Number of Cases Demonstrating "Positive Results" with Respect to Defect Fill

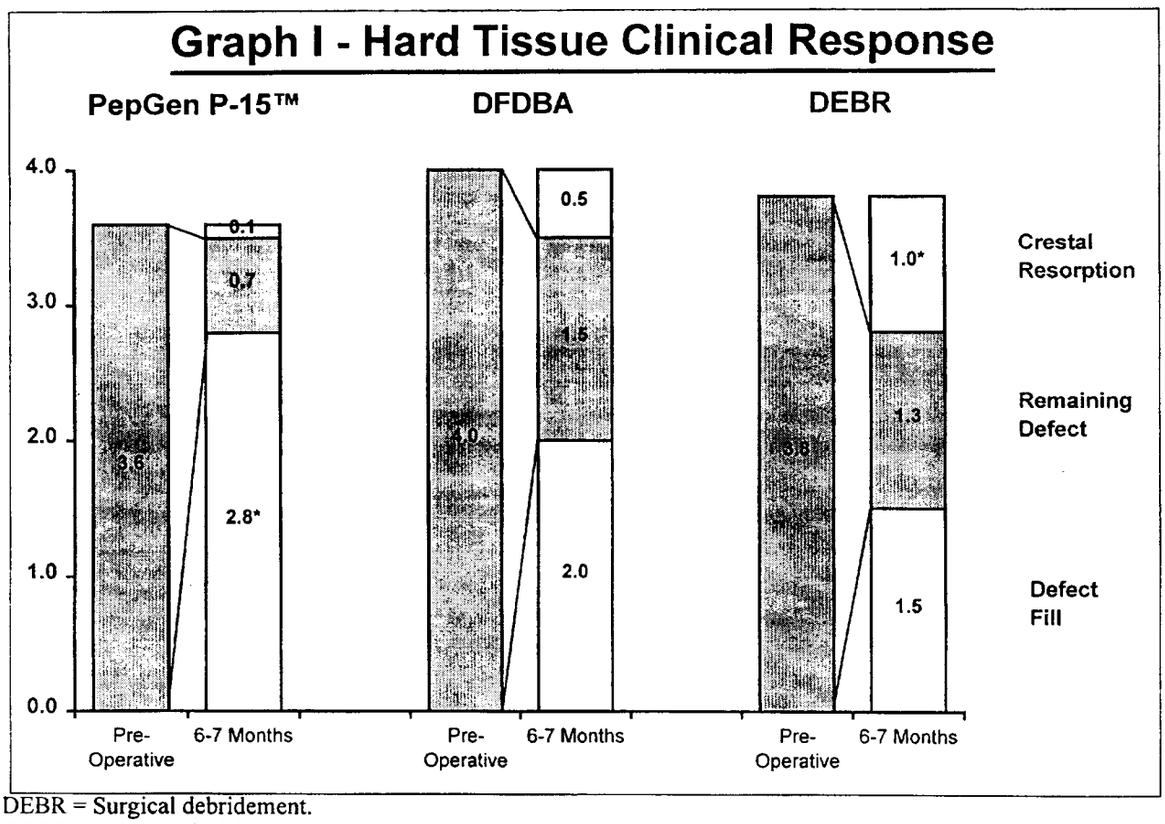
Treatment		≥90% N=31	≥50% N=31	<50% N=31	<20% N=31	% Successful*
PepGen P-15	Number	9	18	4	0	**87%**
	Percent	29	58	13	0	
DFDBA	Number	5	13	4	9	**58%**
	Percent	16	42	13	29	
DEBR	Number	2	11	10	8	**41%**
	Percent	6	35	32	26	

CS-300 = PepGen P-15 (formerly known as OsteoGraf CS-300).
DFDBA = decalcified freeze-dried bone allograft.
DEBR = defect debridement (no graft material).

Treatment success is defined as ≥50% defect fill.

Table III demonstrates the percentage of cases in this study having greater than 50% defect fill using the three treatment modalities studied, as well as cases having less than 50% defect fill. Fifty percent defect fill has been historically viewed as the cutoff point for treatment success because studies in the past have not been able to demonstrate a predictable defect fill greater that approximately 50%. The data in Study #1 indicates that 87% of the PepGen P-15 cases demonstrated a greater than 50% defect fill 87 percent of the time. At the same time, decalcified freeze-dried bone allograft (DFDBA), the benchmark grafting material; the grafting material against which grafting materials are compared, produced a greater that 50% defect fill, 58% of the time.

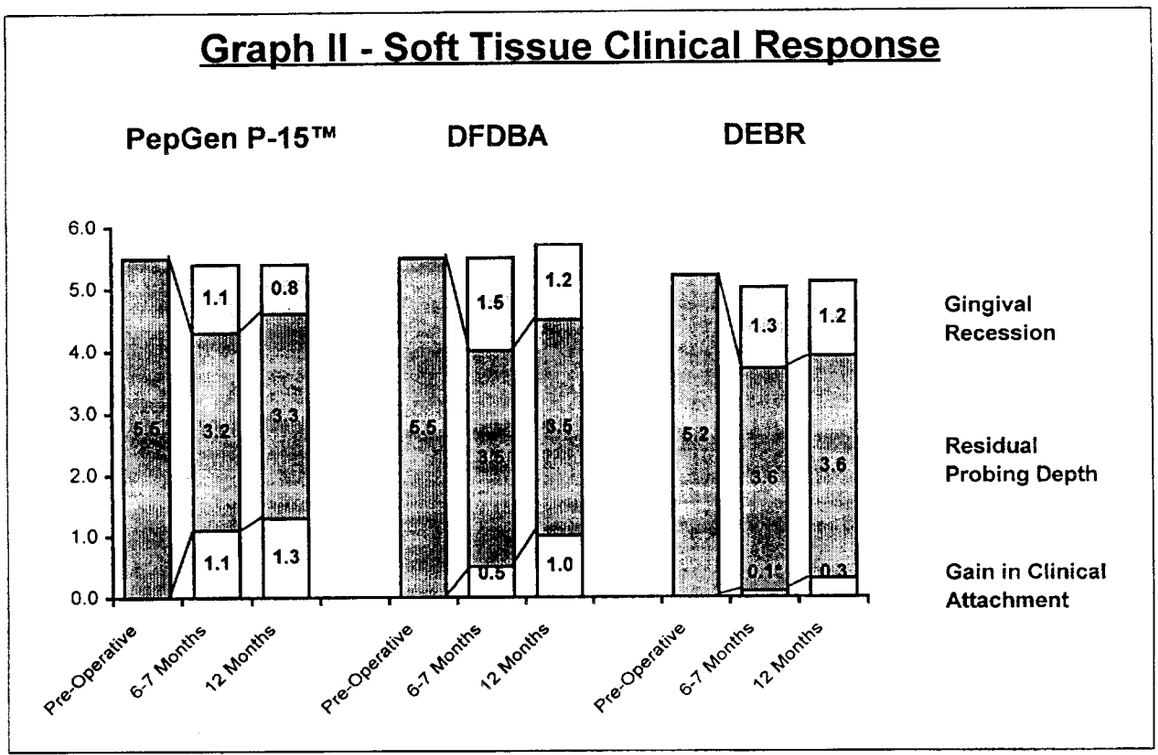
Graphical representations of the typical or average periodontal defect are presented below. The defects and how they responded to the three treatment modalities used in this study give the clinician an idea of what to expect when treating patients. The first bar represents the pre-operative intrabony defect in a treatment arm, and the second bar represents the breakdown of how that defect responded to that particular treatment. Three events occur to varying extents. Resorption of the alveolar crest (net loss of bone) may occur. The defect could be filled partially or fully with bone. Or, the defect could have residual post-surgical probing depth. The second and third bars in each treatment arm indicate what occurred.



DEBR = Surgical debridement.
DFDBA = Decalcified freeze-dried bone allograft.

The asterisks indicate **statistically significant differences**.

Graph #1 displays the osseous response from Study #1, to debridement alone, debridement followed by grafting with freeze-dried bone allograft, or debridement followed by grafting with PepGen P-15. Osseous defect fill was greater, while the amount of defect remaining after treatment, and alveolar crestal resorption, were less using PepGen P-15, than the other two treatments.



DEBR = Surgical debridement
DFDBA = Decalcified freeze-dried bone allograft

Graph II displays the soft tissue response to the above treatment regimens. There appeared to be a small gain in clinical attachment using PepGen P-15 over the other treatments.

Clinical attachment is measured as the algebraic sum of gingival recession and pocket probing depth. It is different than histological attachment level where pocket depth measurements are made using biopsy specimens. Clinical attachment level is measured using a periodontal probe. Histological measurements were not made in either Study #1 or Study #2. The differences observed between histological pocket depth and clinical pocket depth measurements are due to measurement error when using a periodontal probe. The probe tip may not reach the epithelial attachment to the tooth in cases of excellent periodontal health. In cases of inflammation, the probe has been shown to penetrate the junctional epithelium. Residual probing depth, generally referred to as "postsurgical pocket probing depth", was remarkably similar in all three treatment groups. This indicates that, although the bony

support for a tooth may be increased, using some of these treatment modalities more than others, resolution of the periodontal pocket, which is a goal of periodontal therapy, has yet to be accomplished with predictability using any of these treatment modalities.

Study #2

The second clinical study was undertaken to determine the clinical utility or usefulness of adding the P-15 peptide to the OsteoGraf N-300 product in order to create PepGen P-15. This study compared PepGen P-15 to anorganic bovine bone in the form of OsteoGraf N-300, which has been on the market for several years. As in the first study, criteria for success included at least 1 mm difference in clinical probing attachment gain, decrease in probing depth, and defect fill. Percent defect fill and percent decrease in probing depth, were also the same secondary endpoints, used in Study #1. The only difference between the two bone fillers is the presence of the synthetic Type I collagen peptide analogue, P-15. Thirty three patients were studied, and included 12 males and 21 females. Patient age ranged form 38 to 81, and had a mean of 48.7 years. The study results demonstrated statistically significant improvement in percent defect fill, when using PepGen P-15, as compared to OsteoGraf N-300. As in Study #1, all criteria for success were met. PepGen P-15 had a percent defect fill value greater than the 15% found using OsteoGraf N-300, as determined by comparing the measurements taken at the time of initial surgery and the 6-month reentry surgery.

Table IV – Primary Study Outcomes

Responses to Treatment of Human Osseous Defects
Comparison of PepGen P-15 to OsteoGraf N-300

Reentry at 6-7 months

Clinical Parameter	PepGen P-15 N=33	OsteoGraf N-300 N=33	P*
Original Bone Defect (mm)	4.0±0.8	4.3±1.0	NS
Residual Bone Defect (mm)	0.9±1.0	1.5±0.9	SSD
Amount Defect Fill (mm)	2.9±1.2	2.2±1.4	SSD
Percent Defect Fill	72.9±23.3	50.6±26.9	SSD
Crestal Resorption (mm)	0.2±1.0	0.7±1.1	NS#
Percent Defect Resolved	78.4±21.2	65.3±21.4	SSD
Presurgical Pocket Depth (mm)	6.2±1.2	6.0±1.0	NS
Postsurgical Pocket depth (mm)	3.0±1.1	3.3±1.1	NS
Decrease in Pocket Depth (mm)	3.2±1.5	2.9±2.0	NS
Gingival Recession (mm)	1.0±1.4	0.7±1.2	NS
Clinical Attachment Gain (mm)	12.2±2.0	2.1±1.8	NS

- approaches significance
NS – not significant

SSD - p≤0.05 both t test and Mann Whitney U test

Table IV demonstrates that hard tissue findings, such as the differences in amount of defect fill and percent defect fill were statistically, but not clinically significant. The 0.7 mm difference in the amount of defect fill (2.9±1.2 vs. 2.2± 1.4 mm). This measurement is at or just above the measurements considered to be within the range of measurement error generally observed in using a manual periodontal probe. In addition, the difference in alveolar crestal resorption between PepGen P-15 and OsteoGraf N-300 approached, but was not statistically significant. However, the data did appear to favor the use of PepGen P-15. The improvement in percent defect fill of 22.3% is also statistically significant and an improvement in resolution of these defects. There were no significant differences between the two bone fillers with respect to soft tissue parameters.

Table V - Overall Relative Periodontal Defect Fill Success Rate

Treatment	Patients	≥90%	≥50%	<50%	≤20%	% Successful
PepGen P-15	Number	11	16	4	2	81%
	Percent	33	48	12	6	
OsteoGraf N-300	Number	3	19	7	4	67%
	Percent	9	58	21	12	

Table V demonstrates that in Study #2, a greater percentage (≈81% vs. 67%) of periodontal defects exhibited more than 50% defect fill. It is also interesting to note that fewer cases (≈18% vs. 33%) had less than 50% defect fill occurred using PepGen P-15. A success rate of ≥ 50 % to 60% bone fill in ≥50 % of cases studied, has been used as a benchmark for success in grafting of periodontal bony defects within the periodontal clinical community.

Table VI - Comparative Defect Fill by Bone Defect Type
(Cases Treated Using PepGen P-15 vs. OsteoGraf N-300)

Defect Type	N	≥90% Fill	≥50% Fill	<50% Fill	<20% Fill
3 Wall	11/11	3/2	5/6	1/1	2/2
2 Wall	5/3	1/0	3/2	1/1	0/0
1 Wall	3/4	1/1	2/1	0/2	0/0
2-3 Wall	8/6	4/0	4/3	0/2	0/1
1-3 Wall	2/2	1/0	1/2	0/0	/00
1-2 Wall	1/7	0/0	0/5	1/1	0/1
1-2-3 Wall	3/0	1/0	1/0	1/0	0/0
Total	33/33	11/3	16/19	4/7	2/4
Percent Fill		33%/9%	48%/58%	12%/21%	6%/12%
Percent ≥50% Fill		81%/67%		18%/33%	

The percentages indicate the percentage defect fill. The first number in each cell is the number of cases where PepGen P-15 was used, and the second number in each cell is the number of cases where OsteoGraf N-300 was used.

Table VI indicates that both grafting materials demonstrated defect fill. There was a greater percentage of cases treated successfully (81% vs. 67%) when clinical success is defined as ≥50 % defect filled. In addition, there were fewer failed cases (<50% defect fill) using PepGen P-15 (18% vs. 33%), than OsteoGraf N-300.

12. **Conclusions Drawn From Studies**

a. The two multicenter randomly controlled clinical studies described herein, demonstrated the safety and effectiveness of PepGen P15 for the treatment intrabony periodontal osseous defects due to moderate to severe periodontitis.
b. Clinical utility for the addition of P-15 to OsteoGraf N-300 to form PepGen P-15 has been established.

13. **Panel Recommendation**

At an advisory meeting held on January 12, 1998, the Devices Panel recommended that CeraMed's PMA for PepGen P-15 be considered approvable subject to submission of additional data from a postmarket study comparing the PepGen P-15 to the matrix without P-15 (OsteoGraf N-300).

14. FDA Decision - FDA approval is approvable.

CDRH disagreed with the Dental Devices Panel approvable recommendation. However, CDRH concurred with the need for the second clinical study proposed by the Panel. CDRH determined that the PMA was not approvable until the second clinical study was completed, and the results demonstrated a clinical utility for the P-15 peptide component. A not approvable letter was issued February 5, 1998. The applicant responded to the not approvable letter on June 24, 1999 and a new PMA number was issued. It was determined that a second Dental Devices Panel meeting was not necessary for review of the new clinical data. The second clinical study adequately addresses the Panel and FDA concerns about the clinical utility of the P-15 component of PepGen P-15.

FDA determined that the applicant's manufacturing facilities were in compliance with Quality Systems Regulations. In amendment #6, the sponsor withdrew the sterilization contractor because that contractor was no longer performing the type of sterilization services needed by the sponsor. The sponsor stated that they would not have any product sterilized after 10 September, 1999. In the approval order, the applicant was advised that any new sterilization contractor would have to be inspected and approved by FDA, prior to sterilizing or shipping any devices sterilized by the new sterilization contractor.

The approval order was issued on OCT 25 1999.

15. **Approval Specification**

- Instructions for Use: See product labeling.
- Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Cautions, and Adverse Events described in the labeling.
- Postapproval requirements and restrictions (see approval order).

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