SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name: Injectable Dermal Filler

Device Trade Name: RADIESSE®

Applicant's Name and Address: BioForm Medical, Inc.
1875 South Grant Street
Suite 110
San Mateo, CA 94402

Pre-Market Approval
Application Number: P050052

Date of Panel Recommendation: August 24, 2006

Date of Notice of Approval to the Applicant: December 22, 2006

II. INDICATIONS FOR USE

RADIESSE is indicated for subdermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds.

III. CONTRAINDICATIONS

RADIESSE is contraindicated for patients with severe allergies manifested by a history of anaphylaxis, or history or presence of multiple severe allergies.

RADIESSE is not to be used in patients with known hypersensitivity to any of the components.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Radiesse physician's labeling.

V. DEVICE DESCRIPTION

RADIESSE is a sterile, non-pyrogenic, semi-solid, cohesive implant, whose principle component is synthetic calcium hydroxylapatite suspended in a gel carrier of sterile water for injection, glycerin and sodium carboxymethylcellulose. RADIESSE (1.3 cc and 0.3 cc) has a CaHA particle size range of 25-45 microns and should be injected with a 25 to 27 gauge needle.

VI. ALTERNATE PRACTICES AND PROCEDURES

Alternative therapies for dermal soft tissue augmentation permanent implants or other injectable dermal fillers. Additional options for the correction of fine lines and wrinkles include chemical peels, laser skin resurfacing, dermabrasion, botulinum toxin injections, and surgical intervention, i.e., facelift, or no treatment at all.

VII. MARKETING HISTORY

RADIESSE is currently marketed in Europe, Canada and South America. RADIESSE has not been withdrawn from marketing for any reason.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Tables 1-4 contains the adverse events for 117 patients in a randomized, controlled study at 4 US investigational sites. Patients in the study received RADIESSE in one side of the face and a collagen dermal implant as the Control in the other side of the face. Adverse events reported in patient diaries during the 14 days after treatment are listed in Tables 1 and 2. Physician reported adverse events are those reported by Investigators and patients any time outside the 2 week diaries. Those adverse events are presented in Tables 3 and 4.

Table 1: Adverse Events Reported Through Patient Diaries
Number of Patients With at Least One Adverse Event
By Adverse Event Type (N = 117)

	RADIESSE	Control
	Total Reporting Symptoms N(%)	Total Reporting Symptoms N(%)
Ecchymosis	74 (63.2)	50 (42.7)
Edema	81 (69.2)	62 (53.0)
Erythema	78 (66.7)	84 (71.8)
Granuloma	0 (0.0)	0 (0.0)
Needle Jamming	0 (0.0)	0 (0.0)
Nodule	1 (0.9)	1 (0.9)
Pain	33 (28.2)	26 (22.2)
Pruritis	21 (18.0)	24 (20.5)
Other*	35 (29.9)	26 (22.2)

* "Other" adverse events for both Radiesse and Control include soreness, numbness, contour irregularity tenderness and irritation. None of the reports of contour irregularities was determined to be nodules or granulomas.

There were 12 systemic adverse events reported for 9 patients. None of these systemic adverse events were related to either Radiesse or Control and included emergency gallbladder surgery, breast pain, infected and exposed breast

implant, gastroenteritis, uterine fibroids, headache, burning and numbness in tongue and lips, tongue ulceration and fatigue.

Table 2:
Physician Reported Adverse Events
By Adverse Event Type

	RADIESSE	Control	RADIESSE				Control			
	Total Reporting Symptoms N(%)	Total Reporting Symptoms N(%)	Number of Days				Number of Days			
			1 -3 N(%)	4-7 N(%)	8-14 N(%)	>14 N(%)	1-3 N(%)	4-7 N(%)	8-14 N(%)	>14 N(%)
Ecchymosis	91 (60.3)	60 (39.7)	16 (10.6)	37 (24.5)	33 (21.9)	5 (3.3)	15 (9.9)	29 (19.2)	12 (7.9)	4 (2.6)
Edema	104 (54.5)	87 (45.5)	34 (17.8)	43 (22.5)	17 (8.9)	10 (5.2)	34 (17.8)	39 (20.4)	10 (5.2)	4 (2.1)
Erythema	105 (45.1)	128 (54.9)	39 (16.7)	26 (11.2)	19 (8.2)	21 (9.0)	45 (19.3)	35 (15.0)	16 (6.9)	32 (13.7)
Granuloma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Needle Jamming	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nodule	1 (50.0)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)
Pain	40 (54.8)	33 (45.2)	22 (30.1)	13 (17.8)	4 (5.5)	1 (1.4)	20 (27.4)	10 (13.7)	2 (2.7)	1 (1.4)
Pruritis	24 (47.1)	27 (52.9)	15 (29.4)	5 (9.8)	3 (5.9)	1 (2.0)	11 (21.6)	10 (19.6)	3 (5.9)	3 (5.9)
Other	52 (56.5)	40 (43.5)	15 (16.3)	17 (18.5)	8 (8.7)	12 (13.0)	8 (8.7)	10 (10.9)	11 (12.0)	11 (12.0)

Table 3:
Physician Reported Adverse Events
Number of Patients With at Least One Adverse Event
By Adverse Event Type
N = 117

	RADIESSE	Control
	Total Reporting Symptoms N (%)	Total Reporting Symptoms N (%)
Ecchymosis	0 (0.0)	2 (1.7)
Edema	5 (4.3)	4 (3.4)
Erythema	6 (5.1)	9 (7.7)
Granuloma	0 (0.0)	0 (0.0)
Needle Jamming	1 (0.9)	0 (0.0)
Nodule	0 (0.0)	2 (1.7)
Pain	2 (1.7)	1 (0.9)
Pruritis	1 (0.9)	2 (1.7)
Other*	3 (2.6)	3 (2.6)

* "Other" adverse events for both Radiesse and Control include soreness, numbness, contour irregularity tenderness and irritation. None of the reports of contour irregularities was determined to be nodules or granulomas.

Table 4:
Physician Reported Adverse Events
By Adverse Event Type N = 117

	RADIESSE	Control	RADIESSE				Control			
	Total Reporting Symptoms N(%)	Total Reporting Symptoms N(%)	Number of Days				Number of Days			
			1 -3 N(%)	4-7 N(%)	8-14 N(%)	>14 N(%)	1-3 N(%)	4-7 N(%)	8-14 N(%)	>14 N(%)
Ecchymosis	0 (0.0)	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	1 (50.0)	0 (0.0)
Edema	5 (41.7)	7 (58.3)	5 (41.7)	0 (0.0)	0 (0.0)	0 (0.0)	5 (41.7)	0 (0.0)	0 (0.0)	2 (16.7)
Erythema	9 (42.9)	12 (57.1)	4 (19.0)	2 (9.5)	2 (9.5)	1 (4.8)	2 (9.5)	3 (14.3)	4 (19.0)	3 (14.3)
Granuloma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Needle Jamming	1 (100.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nodule	0 (0.0)	3 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	2 (66.7)
Pain	3 (75.0)	1 (25.0)	1 (25.0)	1 (25.0)	0 (0.0)	1 (25.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pruritis	1 (33.3)	2 (66.7)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	1 (33.3)	0 (0.0)	1 (33.3)	0 (0.0)
Other	4 (50.0)	4 (50.0)	1 (12.5)	0 (0.0)	2 (25.0)	1 (12.5)	1 (12.5)	1 (12.5)	0 (0.0)	2 (25.0)

IX. SUMMARY OF PRECLINICAL STUDIES

A. Bench Testing

The following bench tests were conducted to evaluate the performance characteristics of final, packaged and sterilized RADIESSE.

Injection Testing - RADIESSE can be extruded in one minute with an average force of <15 lbsf.

Syringe Leakage - Safety testing demonstrated that the syringe, injection needle or the syringe Luer cap would not rupture with the maximum hand pressure of 30 pounds force (133 Newtons) applied to the syringe push rod using the finger grips.

Simulated Use Testing - RADIESSE, as prepared for injection in primed injection needles, remained functional after twelve hours at room conditions.

Particle Durability - The particles of CaHA remained unchanged after being injected to all processing (including sterilization) and after implantation injection.

Environmental Exposure - RADIESSE has been subjected to temperature extremes including multiple freezing cycles and heat exposures including two years at 45°C (113°F) without loss of functionality.

B. Sterilization and Shelf-life Testing

Steam sterilization of RADIESSE filled syringes was validated to provide a sterility assurance level (SAL) of 10^{-6}. Testing performed on finished product verified that endotoxin levels are consistently maintained. The heat-sealing of the foil pouches has been validated and demonstrated to produce consistent seals with peel strengths of 5 pounds force. Real time and accelerated testing on RADIESSE syringes support a shelf life of three years.

C. Biocompatibility Testing

RADIESSE was subjected to *in-vitro* and *in-vivo* testing based on ISO10993 (Biological Evaluation of Medical Devices), using historically accepted test methods of biomedical materials or United States Pharmacopoeia references in accordance with GLP regulations. Test results showed no evidence that RADIESSE was toxic or mutagenic. Although there was a positive hemolytic result during testing, it has been shown this is attributed to the glycerin found in the aqueous gel vehicle.

In-vivo tests assessed sensitization, irritation, tissue reaction during short-term implantation, systemic reactions, and long-term safety. There was no evidence of antigenicity, irritation, or toxicity.

D. Animal Studies

Various animal studies evaluating RADIESSE in dermal soft tissue augmentation have been conducted that include the product injected into the dermis and subdermis in various animal models as well as a canine study involving soft tissue augmentation of the urinary sphincter.

- Subdermal Filler Materials in Yucatan Mini-Pig – 28 Days

RADIESSE was injected subdermally at sites parallel to the lumbar region of the vertebral column of the animal. At 28 days, the animals were sacrificed and the subdermal tissue was visually examined and then prepared for histological examination. None showed evidence of adverse tissue reactions.

- Local and Systemic Effects in Rabbits – 6 Months

New Zealand White rabbits were injected subdermally with 0.25cc of RADIESSE, Coaptite and the gel carrier component alone (same gel carrier for both RADIESSE and Coaptite). Animals were evaluated at 3 and 6 months after injection, which included urinalysis, hematology, clinical chemistry, macroscopic observations, general health and histological evaluation. All animals were normal macroscopically with no evidence of migration or local reaction. No lymph nodes in the area draining the injection sites were enlarged or detected. None of the test articles including RADIESSE showed evidence of migration, capsule formation or adverse reactions.

- Durability and Absorption Profile in a Canine Model – 32 Weeks

The study evaluated the durability and absorption profile of RADIESSE, when injected into the intradermal and subdermal tissues 12 canines. Animals were sacrificed and evaluated at 4, 8, 12, 16, 24 and 32 weeks after injection. The local reactions were transient and not considered unusual for an injected dermal filler material. At 32 weeks no erythema or edema was observed. There was no evidence of migration of RADIESSE from the injection site and the lymphatic vessels were unremarkable.

- Durability and Absorption Profile in a Yucatan Mini-Pig Model – 32 Weeks

The study evaluated various dermal fillers in the swine model when injected intradermally and subdermally in the Yucatan Mini-Pig. Eleven animals were injected and animals were sacrificed and evaluated at 4, 8, 12, 16, 24 and 32 weeks after injection. The local reaction scores were transient. At 32 weeks no erythema or edema was observed for any of the test articles.

- Evaluation of Urinary Sphincter Augmentation Implantation in Dogs – 3 Years

The product was injected the urinary bladder neck in 24 female mongrel dogs. Twelve additional female dogs were similarly injected with only the gel carrier component as the control. Blood and urine samples were collected from each animal prior to study initiation, prior to termination and at 6-month intervals for animals through the 36-month test period. Designated animals were removed from the study at 1, 3, 6, 12, 25 and 36 months. Each was necropsied; injection sites and other tissue inspected grossly, and implant sites and selected tissues processed for microscopic examination.

Microscopic evaluation of the implant sites at 1, 3, 6 and 12 months revealed a simple macrophage clearing response was associated with the gel carrier. The presence of the test article caused no reaction in the adjacent tissues. The CaHA particles from 1 through 36 months remained encapsulated with no evidence of migration from the injection site. The beginning of CaHA particle disintegration was present in several 25 and 36-month tissue specimens as the particles were being engulfed and solubilized 'in situ' by macrophages at the site. Many other particles remained intact.

IX. SUMMARY OF CLINICAL STUDIES

Study design
The safety and effectiveness of RADIESSE for the treatment of nasolabial folds (NLFs) was evaluated in a multi-center, prospective, randomized clinical trial. Patients were randomized to receive RADIESSE in one fold and a commercially available collagen implant in the contra-lateral fold.

Patients were eligible to receive up to three injections during the initial treatment phase (week 0, week 2 and week 4). At 2 weeks after each treatment, the level of correction was determined and if correction was less than optimal, the Investigator re-treated the nasolabial fold using the same respective treatment materials as in the initial treatment. A safety follow-up was conducted 1 month after any injection and at 3 and 6 months after the last injection. Effectiveness evaluations were conducted at 3 and 6 months after

the last injection. Three blinded reviewers independently evaluated the severity of the subjects nasolabial folds using a validated 6-point wrinkle severity scale.

Study Endpoints

The primary effectiveness endpoint of the study was the blinded reviewers' Lemperle Rating Scale (LRS) score of wrinkle severity at 3 months after the last touch-up (at which optimal correction was achieved). In this assessment, LRS scores were determined, (using this validated 6-point scale), via blinded, photographic assessments by 3 board certified physicians. A change in LRS of 1 was considered to be clinically significant. Secondary effectiveness endpoints included the blinded reviewers' assessment of wrinkle severity at 6 months after treatment, and the volume of material injected.

Study Population

A total of 117 subjects (31-76 years of age) were randomized and treated and 115 (98.3%) completed the 3 month primary effectiveness evaluation and 113 (96.6%) completed the 6 month follow-up visit. The baseline demographics of the study population are presented in Table 5.

Table 5
Patient Demographics, Nasolabial Folds
N = 117

Age (Years)	
Mean	54.7
Standard Deviation	8.9
Minimum	31.0
Maximum	76.0
Gender	
Female	105 (89.7%)
Male	12 (10.3%)
Race	
American Indian	0 (0.0%)
Asian	0 (0.0%)
Black	2 (1.7%)
Caucasian	102 (87.2%)
Hispanic	11 (9.4%)
Other	2 (1.7%)
Smoking History	
Quit Smoking	26 (22.2%)
Never Smoked	83 (70.0%)
Smokes	8 (6.8%)

As indicated in Table 5, the study enrolled a population of predominantly female, Caucasian non-smokers.

Treatment Material Delivered

Volumes injected during the initial treatment phase are detailed in Table 6 below. The total mean volume for RADIESSE was 1.2mL and 2.4mL for the Control.

Table 6
Total Volume of Material Injected (mL), Nasolabial Folds
N = 117

	RADIESSE	Control
Mean	1.2	2.4
Median	1.1	2.2
Standard Deviation	0.5	0.9
Minimum	0.3	0.8
Maximum	2.7	4.7

Effectiveness Results:

Table 7 contains the mean LRS at baseline, 3 months and 6 months for the RADIESSE treated nasolabial folds and the Control treated nasolabial folds with the difference between the means. Baseline scores for the Radiesse and Control groups were not statistically different.

Table 7
Comparison of Mean LRS Scores* for RADIESSE and Control Nasolabial Folds - Baseline, 3 and 6 Months

	RADIESSE	Control	Difference
Baseline	3.4	3.4	0.0
3 Months	1.9	3.5	1.6
6 Months	2.1	3.4	1.3

*Grading Scale: 0=No wrinkles, 1 = Just perceptible wrinkle, 2 = Shallow wrinkle, 3 = Moderately deep wrinkle, 4 = Deep wrinkle, well-defined edges, 5 = Very deep wrinkle, redundant fold

Primary Effectiveness Endpoint

The primary effectiveness endpoint was to use mean LRS scores to evaluate whether RADIESSE was non-inferior to Control for the correction of nasolabial folds 3 months after final treatment. At 3 months, 84.6% of the RADIESSE treated nasolabial folds were scored at least 1-point higher than the Control, 12.8% were scored equally, and 2.6% were scored at least 1-point lower than the Control. RADIESSE met the statistical criteria for non-inferiority to Control at 3 months ($p<0.0001$), however, the Control scored no effectiveness at 3 months.

Secondary Effectiveness Endpoint

The pre-specified secondary superiority analyses at 6 months required a mean 1-point LRS difference between the improvements for the RADIESSE treated nasolabial fold versus improvement on the Control treated nasolabial fold and that in at least 50% of patients, the RADIESSE treated nasolabial fold be superior to the Control treated nasolabial fold. At 6 months after optimal correction was achieved, 78.6% of the RADIESSE-treated nasolabial folds were scored at least 1-point higher than the Control-treated folds,16.2% were scored equally, and 5.1% were scored at least 1-point lower than the Control. The mean LRS for the RADIESSE-treated nasolabial folds demonstrated superiority when compared to the mean LRS for the Control-treated nasolabial folds at 6 months ($p<0.0001$).

Short Term and Long Term Radiographic Evaluation of RADIESSE

RADIESSE contains calcium hydroxylapatite particles (25-45 microns) that are radiopaque and suspended in a water based gel. Therefore a radiographic study was conducted to assess the radiographic appearance of RADIESSE in patients with both

short-term and long-term follow-up after injection for HIV-associated facial lipoatrophy and treatment of nasolabial folds. The radiographic assessment consisted of standard, plain radiography and CT scanning. X-rays and CT Scans were assessed by two blinded, licensed radiologists. The inclusion of these patients allowed assessment of patients immediately after initial injection, at least 12 months after initial injection and patients with varying volumes of RADIESSE implanted.

A total of 58 patients in three patients groups were enrolled into the study. RADIESSE was determined to be visualizable in the X-ray radiographs by both evaluators, but the X-ray readings were not conclusive for the presence of RADIESSE, when in fact it was present. This may be due to the fact that the volume of RADIESSE in some patients was small and the sensitivity of X-ray imaging may not be sufficient to detect small volumes of RADIESSE. RADIESSE was more readily visualizable by CT Scan when compared to X-ray and the CT Scan results were read more consistently between two evaluators. RADIESSE was easily seen when imaging was done soon after an injection and was also seen when imaging was done several months after injection (minimum of 12 months). As expected, the results for the CT Scan provided a superior image capability as compared to X-ray when visualizing Radiesse.

X. CONCLUSIONS DRAWN FROM STUDIES

- In a prospective, randomized, clinical study the device was shown to be non-inferior to the comparator at three months and superior to the comparator at six months based on the LRS (Lemperle Rating Scale) as assessed by blinded photographic assessments.

- There were no serious adverse events or patient deaths reported during the course of the study.

- RADIESSE is seen on both X-ray and CT Scan; however it is unlikely that the presence RADIESSE will mask underlying structures or abnormal growths in the areas in which it is injected.

- There was no evidence of RADIESSE migration.

- Patients, injecting physicians and other medical professionals should be made aware of the radiographic appearance of RADIESSE when injected in the facial area.

XI. PANEL RECOMMENDATIONS:

On August 24, 2006 the General and Plastic Surgery Devices Panel recommended approval with conditions for BioForm Medicals PMA for Radiesse. The conditions of approval included a postapproval study to assess the duration of effect, timing of repeat treatments and the long-term safety of Radiesse treatment; a second postapproval study to gain an assessment of the likelihood of keloid and/or hypertrophic skin changes in patients with Fitzpatrick Skin Types IV-VI; that the labeling should contain a precaution that Radiesse has not been adequately studied in persons of color; and physician training.

XII. CDRH DECISION:

CDRH concurred with the General and Plastic Surgery Devices Panel recommendation and issued a letter to Bioform Medical, Inc. on October 27, 2006, advising that its PMA was approvable subject to changes recommended by the Panel and required by FDA.

In specific, the sponsor has agreed to:

1) Provide the results of an open-label, postapproval study in 100 patients with Fitzpatrick Skin Types 4, 5 or 6 from five or more U.S. centers who have elected to undergo naso-labial fold treatment with subdermal injection of Radiesse. Patients will be followed for a minimum of 24 weeks with visits for assessment of dermal pigmentation and keloid changes at the site of injection at each follow-up point post-optimal cosmesis. The purpose of the study would be to assess the likelihood of hypertrophic scarring and keloid formation in patients with Fitzpatrick Scale skin types 4, 5, and 6. Safety endpoint assessments of this study are: 1) hypertrophic scarring or keloid formation at the site of injection at 12 and 24 weeks, 2) pigmentation changes at the site of injection compared to adjacent skin, and 3) adverse experience assessment.

2) Provide the results of an open label postapproval study in 100 patients to collect long-term safety information on the use of Radiesse injected into nasolabial folds and the effect of multiple injections. This study will enroll 100 patients and monitor these patients for 3 years after the date of their first treatment with a lost to follow-up that does not exceed 20% of the patients enrolled.

The applicant's manufacturing facility was inspected on October 2 – October 18, 2006, and was found to be in compliance with the Quality Systems Regulation (21 CFR 820).

FDA issued an approval order on December 22, 2006.

XIII. APPROVAL SPECIFICATIONS

Directions for Use: See the labeling

Hazard to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Reactions in the labeling

Post Approval Requirements and Restrictions: see the Approval Order.