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:	P050037
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 restoration and/or correction of the signs of facial fat loss (lipoatrophy) in people with human immunodeficiency virus.

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 professional 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

The alternative treatments include permanent implants, other injectable dermal fillers, 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 RADIESSE has not been withdrawn from marketing for any reason.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

In a prospective, open label study of 100 patients at three U.S. sites, adverse events reported after RADIESSE treatments are provided in Tables 8-11. 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
Number of Patients with Maximal Severity of Local Adverse Events Reported Through Patient Diaries
N = 100

Adverse Event	Patients Reporting Symptoms	Mild N(%)	Moderate N(%)	Severe N(%)
Ecchymosis	64	34/64 (53.1)	25/64 (39.1)	5/64 (7.8)
Edema	99	46/99 (46.5)	49/99 (49.5)	4/99 (4.0)
Erythema	55	32/55 (58.2)	23/55 (41.8)	0/55 (0.0)
Granuloma	0	0/0 (0.0)	0/0 (0.0)	0/0 (0.0)
Nodule	0	0/0 (0.0)	0/0 (0.0)	0/0 (0.0)
Pain	37	24/37 (64.9)	13/37 (35.1)	0/37 (0.0)
Pruritis	21	18/21 (85.7)	3/21 (14.3)	0/21 (0.0)
Other*	43	27/43 (62.8)	15/43 (34.9)	1/43 (2.3)

* "Other" adverse events were those reported that did not fit into the categories detailed the tables above. The most common "Other" adverse event was contour irregularities. Additional "Other" adverse events included numbness, dryness, peeling, burning sensation, whiteheads and rash.

Table 2
Duration of Adverse Events as Reported Through Patient Diaries

	Total Reporting Symptoms	Number of Days			
		1 -3 N(%)	4-7 N(%)	8-14 N(%)	>14 N(%)
Ecchymosis	142	29/142 (20.4%)	51/142 (35.9%)	50/142 (35.2%)	12/142 (8.5%)
Edema	430	205/430 (47.7%)	153/430 (35.6%)	52/430 (12.1%)	20/430 (4.7%)
Erythema	210	114/210 (54.3%)	69/210 (32.9%)	22/210 (10.5%)	5/210 (2.4%)
Pain	110	54/110 (49.1%)	32/110 (29.1%)	18/110 (16.4%)	6/110 (5.5%)
Pruritis	54	28/54 (51.9%)	9/54 (16.7%)	6/54 (11.1%)	11/54 (20.4%)
Other	112	40/112 (35.7%)	19/112 (17.0%)	18/112 (16.1%)	35/112 (31.3%)

Table 3
Maximal Severity of Local Adverse Events
Physician Reported Adverse Events
N = 100

Adverse Event	Total Reporting Symptoms	Mild N(%)	Moderate N(%)	Severe N(%)
Ecchymosis	3	2/3 (66.7)	1/3 (33.3)	0/3 (0.0)
Edema	8	8/8 (100.0)	0/8 (0.0)	0/8 (0.0)
Erythema	3	3/3 (100.0)	0/3 (0.0)	0/3 (0.0)
Granuloma	0	0/0 (0.0)	0/0 (0.0)	0/0 (0.0)
Nodule	0	0/0 (0.0)	0/0 (0.0)	0/0 (0.0)
Pain	2	1/2 (50.0)	0/0 (0.0)	1/2 (50.0)
Pruritis	0	0/0 (0.0)	0/0 (0.0)	0/0 (0.0)
Other*	26	20/26 (76.9)	6/26 (23.1)	0/26 (0.0)

* "Other" adverse events were those reported that did not fit into the categories detailed the tables above. The most common "Other" adverse event was contour irregularities. Additional "Other" adverse events included numbness, dryness, peeling, burning sensation, whiteheads and rash.

Table 4
Duration of Adverse Events
Physician Reported Adverse Events

	Total Reporting Symptoms	Number of Days			
		1 -3 N(%)	4-7 N(%)	8-14 N(%)	>14 N(%)
Ecchymosis	5	3/5 (60.0%)	0/5 (0.0%)	2/5 (40.0%)	0/5 (0.0%)
Edema	13	10/13 (76.9%)	1/13 (7.7%)	1/13 (7.7%)	1/13 (7.7%)
Erythema	4	1/4 (25.0%)	2/4 (50.0%)	0/0 (0.0%)	1/4 (25.0%)
Pain	4	2/4 (50.0%)	0/4 (0.0%)	2/4 (50.0%)	0/4 (0.0%)
Pruritis	0	0/0 (0.0%)	0/0 (0.0%)	0/0 (0.0%)	0/0 (0.0%)
Other	62	27/62 (43.5%)	0/62 (0.0%)	1/62 (1.6%)	34/62 (54.8%)

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.

X. SUMMARY OF CLINICAL STUDIES

STUDY DESIGN

The safety and effectiveness of RADIESSE for the treatment of facial lipoatrophy was evaluated in a prospective, open-label, multi-center study of 100 patients with facial lipoatrophy with human immunodeficiency virus. Patients received an initial treatment (initial injection and an additional injection at 1 month as needed). Six months later, all patients were assessed for the need for a touch up injection. Effectiveness was assessed at 3, 6 and 12 months from initial treatment by means of a Global Aesthetic Improvement Scale (GAIS) rating, cheek skin thickness measurements, and patient satisfaction assessment. Safety was assessed by the recording of adverse events through 12 months.

Study Endpoints

The primary endpoint of the study was to evaluate the correction of lipoatrophy 3 months after treatment by comparing changes from baseline on the GAIS. The GAIS is a 5-category scale (Very much improved, much improved, improved, no change and worse). The secondary endpoints of the study were to evaluate the correction of facial lipoatrophy 6 months after treatment by comparing changes from baseline on the GAIS, and 3 and 6 months after treatment by comparing changes from baseline in cheek skin thickness measurements.

Study Population

The inclusion criteria for the clinical study were that the patient was to be HIV positive, had a CD4 count ≥ 250 /mm^3 and viral load ≤ 5000 copies/mL, had been receiving HAART therapy for a minimum of 3 years, had HIV-associated facial lipoatrophy that

was a grade 2, 3, or 4 on the Facial Lipoatrophy Severity Scale, was at least 18 years of age, signed a written informed consent, understood and accepted the obligation not to receive any other facial procedures or treatment affecting facial lipoatrophy through 12 month follow-up and understood and accepted the obligation and was logistically able to present for all scheduled follow-up visits

The exclusion criteria for the clinical study were patients that had a known bleeding disorder (e.g., thrombocytopenia, thrombasthenia, or von Willebrand's disease), had received or was anticipated to receive antiplatelets, anticoagulants, thrombolytics, vitamin E, anti-inflammatories, interferon, or prednisone from 1 week pre- to 1 month post-injection, was receiving systemic or topical corticosteroids or anabolic steroids, had another medical condition that would preclude study participation or suggested an AIDS diagnosis (e.g., Kaposi sarcoma, recurrent infection, recurrent pneumonia), had received silicone injections, facial tissue augmentation other than collagen, grafting, or any other surgery in the cheek area, had received collagen in the cheek area within the past 6 months, had received over-the-counter wrinkle products (e.g., alpha-hydroxy acids) or prescription treatments (e.g., Renova, Retin-A, microdermabrasion, chemical peels) within 4 weeks prior to study or intended to receive these products and/or treatments during the study, had facial hair that would preclude ability to assess facial lipoatrophy, had a history of keloid formation, was pregnant or lactating or not using a reliable form of birth control, if female of child bearing potential and was enrolled in an interfering study.

Study Results

Demographics / Injection Information:

The study enrolled a population of predominantly multi-ethnic, non-smoking males (94% male) with a mean age of 48 years. Forty-four (44) percent of patients were Black, Hispanic or Asian. Fifty-six (56) percent were Caucasian. Fifty-one (51) percent of patients had a Fitzpatrick Skin score of IV, V or VI. All treatments were performed with a 25 gauge, 1½ inch needle. Mean initial treatment volumes were 4.8mL for the initial treatment and 1.8mL at 1 month if necessary (85% of patients were treated at 1 month). At 6 months, the mean touch up volume was 2.4mL (89% of patients). Four (4) percent of patients received only one treatment, 18% of patients received a total of two treatments and 78% of patients received a total of three treatments. No patient received more than three treatments.

Effectiveness Results:

A live GAIS rating was determined at 3 and 6 months (see Table 5).

Table 5
GAIS Ratings

% of Patients	3 Month N = 100	6 Month N = 98
Very Much Improved	26%	7%
Much Improved	72%	86%
Improved	2%	7%
No Change	0%	0%
Worse	0%	0%
Total	100%	100%

Cheek thickness measurements of patients left and right cheeks were performed at baseline, 3 and 6 months (see Table 6).

Table 6
Cheek Thickness Measurements

	BASELINE	3 MONTH			6 MONTH		
	Mean (N=100)	Mean (N=100)	Δ From Baseline	p-Value	Mean (N=97)	Δ From Baseline	p-Value
Left Cheek	4.7mm	7.3mm	2.6mm	<0.0001	7.1mm	2.4mm	<0.0001
Right Cheek	4.9mm	8.0mm	2.1mm	<0.0001	7.5mm	2.7mm	<0.0001

Patients provided responses to a 5-question patient satisfaction questionnaire at 3 and 6 months (see Table 7).

Table 7
Patient Satisfaction Assessment

	3 Months N = 100	6 Months N = 98
	Yes	Yes
Would you recommend RADIESSE treatment?	99%	99%
Has the RADIESSE treatment been beneficial to you?	100%	100%
Do you feel more attractive since receiving RADIESSE treatment?	98%	98%
Is your emotional wellbeing better since receiving RADIESSE?	91%	96%
Do you have more confidence in your appearance since receiving RADIESSE?	98%	98%

G. 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.

XI. CONCLUSIONS DRAWN FROM THE STUDIES

The submitted clinical data provide a reasonable assurance of the safety and effectiveness of Radiesse for the correction of facial lipoatrophy in people with human immunodeficiency virus. The studies demonstrated that:

In an open-label study of 100 subjects there was significant clinical improvement noted on the GAIS (Global Aesthetic Improvement Scale) at both the three and six month time points.

There were no reported serious adverse events notes during the study. The most common adverse events were ecchymosis, edema, erythema, pain and pruritis.

RADIESSE is seen on both X-ray and CT Scan; 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.

XII. SKIN TYPE AND GENDER BIAS

An important consideration for injectable materials is the effect of the device on various skin types. In this study, the sponsor enrolled a representative sampling of the demographic variables in the US. A larger number of males were enrolled.

XIII. PANEL RECOMMENDATION

On August 24, 2006, the General and Plastic Surgery Devices Panel recommended approval with conditions for BioForm Medical's PMA for Radiesse. The conditions of approval included collection of 18 month follow-up data; a precaution in the label that the device has been studied in HIV+ lipoatrophy patients; and physician training.

XIV. 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 18 month follow-up data on the patients already enrolled in the study to evaluate any adverse events after repeat injections.

2) Provide training to all health care professionals who will be using the device.

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.

XV. 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.