SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	Injectable Dermal Filler
Device Trade Name:	**SCULPTRA™**
Applicant's Name and Address:	Dermik Laboratories A Division of Aventis Pharmaceuticals Inc. 1050 Westlakes Drive Berwyn, PA 19312
Premarket Approval Application (PMA) Number:	P030050
Date of Panel Recommendation:	March 25, 2004
Date of Notice of Approval to the Applicant:	August 3, 2004

II. INDICATIONS FOR USE

SCULPTRA™ is intended for restoration and/or correction of the signs of facial fat loss (lipoatrophy) in people with or receiving treatment for human immunodeficiency virus.

III. CONTRAINDICATIONS

- **SCULPTRA™** should not be used in any person who has hypersensitivity to any of the components of the product.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the **SCULPTRA™** professional labeling.

V. DEVICE DESCRIPTION

SCULPTRA™ is an injectable poly-L-lactic acid implant in the form of a sterile lyophilized cake. **SCULPTRA™** contains microparticles of poly-L-lactic acid, a biocompatible, biodegradable, synthetic polymer from the alpha-hydroxy-acid family. **SCULPTRA™** is reconstituted prior to use by the addition of Sterile Water for Injection, USP (SWFI) to form a sterile non-pyrogenic suspension.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are no products in the US specifically approved for correction of the signs of facial fat loss in patients with lipoatrophy. Alternative therapies that have been used include temporary dermal fillers and permanent implants.

VII. MARKETING HISTORY

SCULPTRA™ (injectable poly-L-lactic acid) was developed in Europe and marketed under the trade name **NEW-FILL™**, with CE Mark certification obtained in 2004, for "large volume correction for the signs of lipoatrophy." The product was initially developed by Biotech Industries S.A. Luxembourg, and was acquired by Dermik Laboratories in May 2002.

NEW-FILL™ is currently marketed in over 30 countries outside the United States. The product will be marketed as **SCULPTRA™** in the US.

NEW-FILL™ has not been withdrawn from any marketplace for any reason related to the safety and effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Adverse event data from four clinical studies that included 277 patients are summarized in Tables 1 & 2.

TABLE 1:
NUMBER OF PATIENTS WITH TREATMENT-RELATED ADVERSE EVENTS OBSERVED IN CLINICAL STUDIES WITH TWO-YEAR FOLLOW-UP

	VEGA STUDY 50 Patients	C&W STUDY 29 Patients	AVERAGE DURATION (DAYS)
INJECTION PROCEDURE RELATED ADVERSE EVENTS			
Bruising	3	11	6
Edema	2	2	3
Discomfort	0	3	3
Hematoma	14	0	17
Inflammation	0	3	3
Erythema	0	3	3
DEVICE-RELATED ADVERSE EVENTS			**AVERAGE ONSET** (Months)**
Injection site subcutaneous papule*	26	9	7

*Subcutaneous papules refer to lesions of 5 mm or less, typically palpable, asymptomatic and non-visible.
**Onset data available from VEGA study only. Duration not noted for subcutaneous papules because most were ongoing at study completion.

TABLE 2:
NUMBER OF PATIENTS WITH TREATMENT-RELATED ADVERSE EVENTS OBSERVED IN CLINICAL STUDIES WITH ONE-YEAR FOLLOW-UP

	APEX 002 STUDY 99 Patients	BLUE PACIFIC STUDY 99 patients
INJECTION PROCEDURE RELATED ADVERSE EVENTS		
Bruising	1 (1%)	30 (30%)
Edema	3 (3%)	17 (17%)
Discomfort	19 (19%)	15 (15%)
Erythema	0	3 (3%)
DEVICE-RELATED ADVERSE EVENTS		
Injection site subcutaneous papule	6 (6%)	13 (13%)

The most common device related adverse effect was the delayed occurrence of subcutaneous papules, which were confined to the injection site and were typically palpable, asymptomatic, and non-visible. The study protocols did not include evaluation of treatment for subcutaneous papules. In the VEGA study, the average onset of subcutaneous papules was 7 months after initial injection (range 0.3 – 25 months). Subcutaneous papules resolved spontaneously in 6/26 patients (24%) during the study.

Treatment related adverse events, not included in Table 1 & 2, observed in clinical studies with a frequency of less than 5% were: injection site tenderness, injection site lesion, injection site bleeding, injection site induration, injection site infection and fever.

The following adverse events, which were not observed in the clinical studies, were detected from post-marketing surveillance and literature reports: visible nodules with or without

inflammation or dyspigmentation, malaise, injection site abscess, allergic reaction, injection site atrophy, Quincke's edema, injection site fat atrophy, photosensitive reaction, fatigue, injection site granuloma, hypersensitivity reaction, skin rash, skin roughness, lack of drug effect, injection site reaction, hypertrophy of skin, hair breakage, colitis not otherwise specified, brittle nails, application site discharge, angioedema, aching joints, ectropion, and telangiectasias.

IX. SUMMARY OF PRECLINICAL STUDIES

The biocompatibility studies comprising this preclinical safety assessment complied with the International Standard ISO 10993-1 Biological Evaluation of Medical Devices. **SCULPTRA™** is considered to be an implant device in permanent (>30 days) contact with tissue/bone. The safety assessment studies completed for this device included: cytotoxicity, sensitization, irritation, systemic toxicity, sub-chronic toxicity, genotoxicity, implantation, hemocompatibility, and pyrogenicity studies. Table 3 below summarizes the results of these studies.

TABLE 3 NONCLINICAL TOXICITY STUDIES OF THE DEVICE PERFORMED IN ACCORDANCE WITH ISO 10993 GUIDELINES

TEST CATEGORY	STUDY RESULTS
Cytotoxicity	Negative.
Sensitization	Negative.
Irritation or Intracutaneous toxicity	Negative.
Systemic Toxicity (Acute)	Negative.
Sub-chronic Toxicity	Negative.
Genotoxicity	Negative.
Implantation (Local Tolerance)	Expected foreign body reaction.
Hemocompatibility	Negative.
Pyrogenicity	Negative.

Based on the long-term safety profile of polylactides in animals and the extensive clinical use, it was concluded that **SCULPTRA™** poses little or no long-term safety risk for the patients; and therefore, chronic toxicity and carcinogenicity studies were not required.

SCULPTRA™ passed all the biocompatibility tests. The preclinical testing indicated that **SCULPTRA™** was safe to be evaluated in clinical studies.

X. SUMMARY OF CLINICAL STUDIES

The clinical basis for approval of this pre-market application is the outcome of four clinical studies. Based upon skin thickness measurements in conjunction with serial photographs as assessed in clinical studies, **SCULPTRA™** was demonstrated to be safe and effective for restoration and/or correction of shape and contour deficiencies resulting from facial fat loss (lipoatrophy) in patients with or receiving treatment for human immunodeficiency virus. Data from four clinical studies are presented below.

VEGA STUDY

Study Design

This was a 96-week, open-label, non-comparative, single-center study to determine the treatment effects of **SCULPTRA™** on the signs of lipoatrophy of the face in 50 patients infected with human immunodeficiency virus. Clinical effectiveness was determined by the measurement of skin thickness measured over the course of the study by ultrasonography in the cheek area at Baseline, Weeks 8, 24, 48, 72 and 96. Additionally, serial photographs were obtained at each visit. Safety was assessed by the collection of adverse events and laboratory measurements.

Patient Population

Patients included in the trial were over 18 years of age, human immunodeficiency virus positive, and were receiving concurrent antiretroviral therapy.

Patients had a mean age of 45 years (range 33-58), 84% were Caucasian and 98% were male. All patients had little or no adipose tissue in cheek area at baseline, indicating severe facial lipoatrophy (mean adipose thickness of 0.5±0.7 mm, ranging from 0.0 to 2.1 mm).

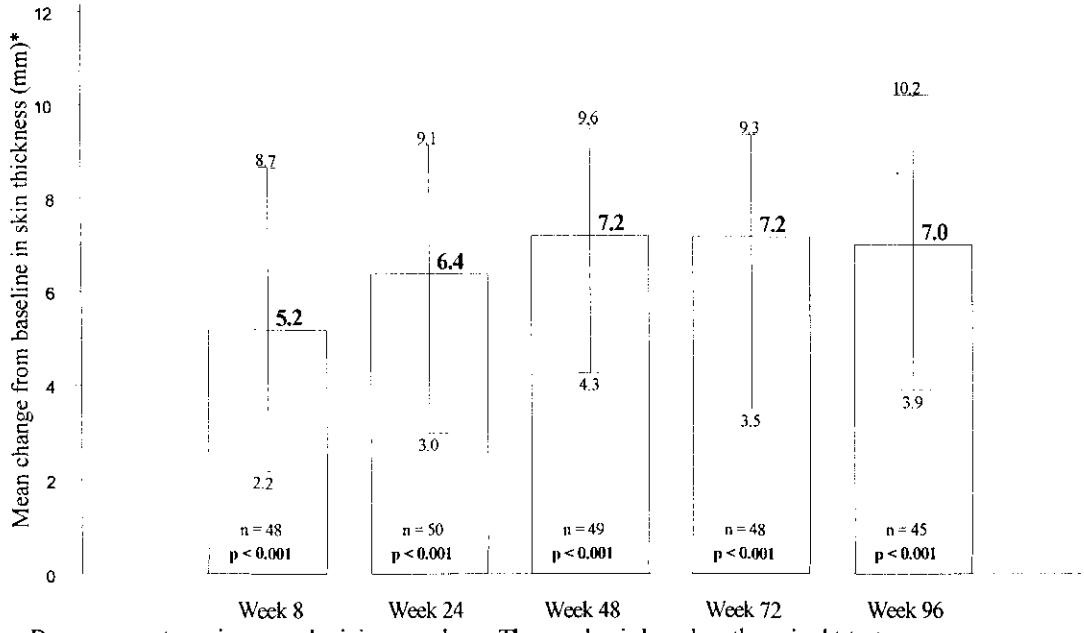
Treatment with the Device

Injection sessions were conducted at approximately two-week intervals, and the majority (86%) of the patients received four to five injection sessions. Generally, one vial of product was injected intradermally into multiple points of each cheek at each injection session. The quantity of injected product and number of injection sessions depended upon the severity of the facial depression.

Results

The mean increases from baseline in skin thickness are presented in Figure 1 below. All patients experienced increases in skin thickness in the treatment area (minimum increase of 2.2 mm noted at Week 8 visit). Significant increases above baseline values of mean skin thickness were noted at all time points (Weeks 8, 24, 48, 72 and 96) during the study. Increases in mean skin thickness changes above baseline persisted for up to 2 years.

FIGURE 1
MEAN INCREASES ABOVE BASELINE IN SKIN THICKNESS (MM) OBSERVED IN THE VEGA STUDY



Bars represent maximum and minimum values; The p-value is based on the paired t-test.
* Baseline = 3.0 ± 0.6 mm

CHELSEA & WESTMINSTER (C&W) STUDY

Study Design

This was a 24-week, open-label, single-center, randomized study in 30 human immunodeficiency virus positive patients with facial lipoatrophy. Patients were randomized to the Delayed Treatment Group (treatment delayed by 12 weeks) or Immediate Treatment Group, and therefore received 12 or 24 weeks, respectively, of follow-up. This design allowed the Delayed Treatment Group to act as a negative control to the Immediate Treatment Group, but still allowed all participating patients to receive treatment for their facial lipoatrophy. For the patients randomized to the Immediate Treatment Group, **SCULPTRA™** injections were administered bilaterally in the cheeks and nasolabial fold areas on Day 1, and at Weeks 2 and 4. After facial ultrasounds were obtained, patients in the Delayed Treatment Group received injections at Weeks 12, 14 and 16 of the study. All patients completed the study at Week 24.

Clinical effectiveness was determined by the measurement of skin thickness measured over the course of the study by ultrasonography in the cheek and nasolabial area at Baseline, Weeks 12 and 24. Ultrasonography of the untreated mouth and zygoma area were included as internal controls. Additionally, serial photographs and anxiety and depression scores from the validated Hospital Anxiety and Depression (HAD) scale were obtained at each visit. Safety was assessed

by the collection of adverse events and laboratory measurements. Additional safety data were collected *post hoc* for 27 of the patients at approximately two years from study start.

Patient Population

Patients included in the trial were over 18 years of age, human immunodeficiency virus positive, and were receiving concurrent antiretroviral therapy. Patients had a mean age of 41 (range 32-60), 72% were Caucasian and 93% were male.

Treatment with the Device

All patients received a fixed treatment regimen of three injection sessions conducted at two-week intervals. Each vial of **SCULPTRA™** was reconstituted with 2 mLs of SWFI and 1 mL of 2% lidocaine to give a total volume of 3 mL. Up to 3 mL of the reconstituted product was injected bilaterally into multiple points into the cheek and nasolabial areas.

Results

Baseline skin thickness in the treatment areas ranged from 2.1 to 2.7 mm. Significant changes from Baseline ($p<0.001$) in mean skin thickness were observed in the areas treated (left and right nasolabial and cheeks) with **SCULPTRA™** in all patients (see Table 4).

TABLE 4
SKIN THICKNESS CHANGES (MM) FROM BASELINE
CHELSEA & WESTMINSTER STUDY

	Immediate Treatment Group N=14 Weeks 12 and 24			**Delayed Treatment Group** N=8 Week 12, N=13 Week 24			
Dermal Thickness (mm)	**Baseline Mean**	**Change from Baseline Mean (SD)**	**Within-Group p-value**	**Baseline Mean**	**Change from Baseline Mean (SD)**	**Within-Group p-value**	**Between-Group p-value**
Left Nasolabial							
Week 12	2.4	3.9 (2.1)	**<0.001**	2.4	0.1 (0.6)	0.774	**<0.001**
Week 24	2.5	5.3 (1.8)	**<0.001**	2.4	5.7 (2.1)	**<0.001**	0.525
Right Nasolabial							
Week 12	2.7	4.3 (2.9)	**<0.001**	2.3	0.2 (0.7)	0.448	**0.001**
Week 24	2.7	4.9 (2.3)	**<0.001**	2.5	6.0 (2.6)	**<0.001**	0.250
Left Cheek							
Week 12	2.4	4.1 (2.8)	**<0.001**	2.1	0.4 (0.4)	0.037	**0.001**
Week 24	2.5	4.9 (1.8)	**<0.001**	2.3	5.7 (1.8)	**<0.001**	0.247
Right Cheek							
Week 12	2.6	3.9 (2.4)	**<0.001**	2.3	0.3 (0.4)	0.121	**<0.001**
Week 24	2.6	4.9 (2.3)	**<0.001**	2.4	5.5 (2.3)	**<0.001**	0.487

Significant changes from Baseline ($p<0.001$) in skin thickness were observed in the areas treated with **SCULPTRA™** (left and right nasolabial and cheeks) at Week 12 and maintained through Week 24 in the Immediate Treatment Group. Areas that were not treated with the product (left and right mouth and zygoma) failed to show improvements in dermal thickness at any time point and therefore acted as an internal control. Significant changes from baseline were not observed until Week 24 (i.e., 12 weeks after initiation of treatment) in the Delayed Treatment Group ($p<0.001$). Thus, the patients in the Delayed Treatment Group acted as a negative control to the

Immediate Treatment Group at the Week 12 time point. As expected, differences in dermal thickness at treated sites were significantly different between groups at Week 12 ($p<0.001$). At Week 24 of the study, there were no differences in dermal thickness between the groups. This indicated that the treatment was equally effective in both groups, regardless of the arm to which they were randomized. A mean increase in dermal thickness of approximately 4-6 mm was observed twelve weeks after the initiation of treatment for both the Immediate Treatment Group (at Week 12), and in the Delayed Treatment Group (at Week 24); see Table 5.

TABLE 5:
RANGE OF MEAN INCREASES IN SKIN THICKNESS FROM BASELINE

	12 WEEKS AFTER 1ST TREATMENT N=27*	24 WEEKS AFTER 1ST TREATMENT N=14*
Cheek Areas	**3.9 – 5.7 mm**	**4.9 mm**
Nasolabial Areas	**3.9 – 6.0 mm**	**4.9 – 5.3 mm**

Baselines ranged from 2.1 to 2.7 mm; all changes were significant ($p<0.001$).
* Number of patients varies due to randomization schedule.

Mean anxiety scores from the validated Hospital Anxiety and Depression (HAD) questionnaire were improved in the Immediate Treatment Group at Weeks 12 and 24. At Baseline, mean HAD anxiety scores were within the range "suggestive of mood disorder" and the decreases in scores brought the patients' mean scores within the range of "normal". Mean HAD depression scores also showed improvements in the Immediate Treatment Group at Weeks 12 and 24 and at Week 24 in the Delayed Treatment Group (after treatment, but not before).

APEX 002 AND BLUE PACIFIC STUDIES

Design of the Studies

Two, single-center, open-label, 12-month investigator-initiated studies were conducted in human immunodeficiency virus positive patients with facial lipoatrophy. Both studies utilized an investigator rating of lipoatrophy and serial photography, as well as patient satisfaction or acceptability with the treatment. In the Blue Pacific study, the investigators additionally measured facial skin thickness with calipers. In both studies laboratory evaluations were performed, and adverse events and concomitant medications were collected. Any discomfort with injections was recorded. Both studies evaluated similar numbers of patients and had follow-up visits at 6 and 12 months post treatment.

Patient Populations

Ninety-nine patients between 31 and 65 years of age were enrolled in each study. The majority of patients were Caucasian males.

Treatment with the Device

Patients were treated with **SCULPTRA™** injections at an interval of approximately 3 to 6 weeks and received up to 6 injection sessions. The average amount of product injected at each injection session was 7.8 mL (APEX 002) and 6 mL (Blue Pacific). It should be noted that these studies allowed treatment of the entire face (e.g., sunken cheeks and temples).

Results

Results and conclusions reported by the investigators for both studies were similar. On a scale of 1 to 5 (1 = dissatisfied to 5 = very satisfied), patients reported an average satisfaction score of 4.7 in APEX 002 and 4.7 in the Blue Pacific study at the end of treatment. Patient satisfaction at 12 months after treatment in APEX 002 showed an average satisfaction score of 4.8.

XI. CONCLUSIONS DRAWN FROM THE STUDIES

The safety and effectiveness of **SCULPTRA™** as a treatment to correct the signs of facial fat loss in patients with lipoatrophy was demonstrated. Data supporting the clinical utility are derived primarily from two prospective clinical studies (VEGA and Chelsea & Westminster), each with extended follow-up periods (up to two years). In these studies, **SCULPTRA™** demonstrated an acceptable safety profile in human immunodeficiency virus seropositive patients. Treatment-related adverse events were generally limited to transient events associated with the immediate injection procedure. Long-term adverse effects, even with a follow-up period of up to two years, were limited to small, asymptomatic subcutaneous papules in the treatment area. The effectiveness of **SCULPTRA™** was clearly demonstrated in these trials. For each study the clinical endpoints were based upon objective measurements of dermal thickness. The studies demonstrated highly significant increases in dermal thickness (up to 2 to 3 times baseline values). In the VEGA study, the increases in dermal thickness throughout the study were also associated with visible corrections of the volume defects as demonstrated by patient photographs (i.e., visible improvement in outward appearance). The clinical utility of **SCULPTRA™** is also supported by improvements in Quality of Life (VEGA study) and self-assessments of facial appearance, as well as measures of anxiety and depression (Chelsea & Westminster study). The results demonstrated in the studies with two-year follow-up have been confirmed with two additional investigator initiated studies (Apex and Blue Pacific) with follow-up periods of one year each. Overall, valid scientific evidence presented in the PMA supports the safety, effectiveness, and clinical utility of **SCULPTRA™** for the correction of signs of facial fat loss in patients with lipoatrophy.

The benefits of use of the device for the target population outweigh the risk of illness or injury when used as indicated in accordance with the directions for use.

XII. SKIN TYPE AND GENDER BIAS

The majority of patients enrolled in the clinical studies were Caucasian, who most commonly represent Fitzpatrick skin types 1 – 3. Minority populations, who more commonly represent Fitzpatrick skin types IV – VI, also comprised a minority of the study group. This proportion is reflective of the general U.S. population that may seek treatment with Sculptra.

Men made up a majority of the patients in the clinical studies. Gender was represented as may be expected in the US market.

XIII. PANEL RECOMMENDATION

The PMA was referred to the General and Plastic Surgery Panel and FDA advisory panel for review and recommendation on March 25, 2004. The panel recommended that the PMA be Approvable with Conditions. The panel recommended the following conditions:

1. The sponsor must conduct a postapproval study of at least 2 years duration that focuses on the issues the panel raised during its discussion, including long-term side effects; adverse events; use in broader populations, including women and minorities; stratification of histological changes; and effects of repeat injections.
2. The sponsor should develop a training program that focuses on quality and technique and emphasizes the indications for use.
3. Use of the product should be restricted to HIV patients with lipoatrophy.
4. Product specifications must be more fully developed and specific and should be based on the final injected product. The characteristics of the final injected product, including molecular weight, crystallinity, particle size distribution, and resorption rate, are most important.
5. The sponsor should make the following changes to the labeling:
   - The intended use should state that the product is only for ". . . facial fat loss, lipoatrophy, caused by HIV or its treatment."
   - The warnings should include a stronger statement about avoiding overcorrection.
   - The labeling should state that safety has been established only in adult male Caucasian populations, and not in pregnant women, infants, or children.
   - Under adverse events, the word "nodules" should be changed to language that is consistent with dermatologic practice.
   - The warning should note that 52 percent of patients have nodule formation and that extreme caution must be exercised in periorbital and perioral areas.
   - The precautions should state that Sculptra should be used only by providers with expertise in correcting defects, and then only after a training program and familiarization of the physician with the product and complete package insert.
   - The labeling should state that performance of Sculptra in patients without HIV disease has not been established and may be hazardous to health.
   - The labeling should state that no studies of drug interactions or of long-term safety and efficacy have been conducted with the product.

CDRH DECISION

CDRH granted expedited review to the PMA application on January 16, 2004 because: 1) the device affects a condition that is irreversibly debilitating; and 2) the device addresses an unmet medical need and is in the best interest of the patients.

CDRH agreed with the panels recommendations, and is approving the PMA with the following condition: the sponsor will conduct a post approval registry study to evaluate the long-term safety of serial injections of Sculptra in a sufficient number of subjects with HIV associated

lipoatrophy to ensure 100 evaluable subjects at 5 years, including at least 30 females and 30 subjects with Fitzpatrick skin types IV-VI.

The sponsor is developing educational materials for health care providers to familiarize them with the use of the device for in patients with HIV associated lipoatrophy.

Based on the preclinical and clinical data in the PMA, CDRH determined the data provide a reasonable assurance that the device is safe and effective when used in accordance with the labeling.

The applicants manufacturing facility was inspected May 24-27, 2004 and was found to be in compliance with the Quality system Regulation (21 CFR 820).

FDA issued an approval order on August 4, 2004.

APPROVAL SPECIFICATIONS

Directions for Use: See product labeling

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

Postapproval Requirement and Restrictions: See the approval order.