SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	Injectable Dermal Filler
Device Trade Name:	Restylane® Injectable Gel
Sponsor's Name and Address:	Q-Med Scadinavia, Inc. 116 Village Boulevard Suite 200 Princeton, NJ 08540
Premarket Approval Application (PMA) Number:	P020023
Date of Panel Recommendation:	November 21, 2003
Date of GMP Inspection:	June 14, 2001
Date of Notice of Approval To the Applicant:	December 12, 2003

II. INDICATIONS FOR USE

Restylane is indicated for mid-to-deep dermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds.

III. CONTRAINDICATIONS

- Restylane is contraindicated for patients with severe allergies manifested by a history of anaphylaxis, or history or presence of multiple severe allergies.
- Restylane contains trace amounts traces of gram positive bacterial proteins, and is contraindicated for patients with a history of allergies to such material.
- Restylane is contraindicated for use in breast augmentation, and for implantation into bone, tendon, ligament, or muscle.
- Restylane must not be implanted into blood vessels. Implantation of Restylane into dermal vessels may cause vascular occlusion, infarction, or embolic phenomena.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Restylane Injectable Gel professional labeling.

V. DEVICE DESCRIPTION

Restylane consists of stabilized, hyaluronic acid (HA) generated by streptococcal bacteria and formulated to a concentration of 20 mg/ml, suspended in a physiological buffer pH 7. Restylane is a transparent, viscous and sterile gel, supplied in a disposable glass syringe. Each syringe contains 0.4 or 0.7 ml gel. The contents of the syringe are sterile. The syringe is equipped with a plunger stopper, finger grip and plunger rod. The syringe is packed in a blister together with a sterile 30 G needle.

The HA has a molecular weight of about 1 million and a protein load of <0.5 EU/ml. The HA formulated in Restylane is stabilized by adding a minimum amount of BDDE to allow formation of a 3-dimensional HA molecular network (gel). The chemical stabilizing process does not change the polyanionic character of the polysaccharide chain. Only about 1% of the polysaccharide has been stabilized.

VI. ALTERNATE PRACTICES AND PROCEDURES

Treatment of photo-damaged skin, with its associated wrinkling and changes in texture and pigmentation, is often accomplished by use of topical creams (containing e.g. retinoids), chemical peeling procedures or laser resurfacing. Deeper wrinkles, folds, scars, and other depressed lesions are often treated with surgery (e.g. rhytidectomi) or by implantation of tissue augmenting substances (e.g. injection of bovine collagen or autologus fat). In these cases, correction of the depression is the goal of therapy.

VII. MARKETING HISTORY

Restylane was first approved for marketing and sale in September 1996 in the European Union, including EES. In 1998 registration was obtained in Canada, Brazil, Hungary and Russia. In 1999 the product was registered in Australia, Argentina, Peru, Poland and Korea. In 2000 it was approved in Ecuador, Mexico, Uruguay, Turkey and Singapore. During 2001 approval was obtained in Bulgaria, Colombia, Czech Republic, Jordan, Slovak Republic and Philippines. During 2002 Restylane was approved in Estonia, Israel, Morocco, Panama and Ukraine. During 2003 the product was approved in India and Taiwan.

The device has not been withdrawn from marketing for any reason related to the safety or effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

In a U.S. study of 138 patients at 6 centers, adverse events reported in patient diaries during 14 days after treatment are listed in Tables 1 and 2 below, while those reported on the physician case report forms are listed in Table 3. Patients in the study received Restylane injections in one side of the face, and a bovine collagen dermal filler (Zyplast) in the other side of the face:

Table 1
Maximum Intensity of Symptoms after Initial Treatment, Patient Diary

	Restylane	**Zyplast side**	**Restylane side**				**Zyplast side**			
	Total reporting symptoms n (%)	Total reporting Symptoms n (%)	None (n%)	Mild n (%)	Moderate n (%)	Severe n (%)	None n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Bruising	72 (52.2)	67 (48.6)	63 (45.6)	32 (23.2)	35 (25.4)	5 (3.6)	68 (49.3)	43 (31.2)	23 (16.7)	1 (0.7)
Redness	117 (84.8)	117 (84.8)	17 (12.3)	56 (40.6)	54 (39.1)	7 (5.1)	17 (12.3)	72 (52.2)	37 (26.8)	8 (5.8)
Swelling	120 (87.0)	102 (73.9)	14 (10.1)	54 (39.1)	61 (44.2)	5 (3.6)	32 (23.2)	65 (47.1)	35 (25.4)	2 (1.4)
Pain	79 (57.2)	58 (42.0)	55 (39.9)	40 (29.0)	34 (24.6)	5 (3.6)	76 (55.1)	46 (33.3)	10 (7.2)	2 (1.4)
Tenderness	107 (77.5)	89 (64.5)	27 (19.6)	60 (43.5)	43 (31.2)	4 (2.9)	45 (32.6)	70 (50.7)	17 (12.3)	2 (1.4)
Itching	42 (30.4)	33 (23.9)	91 (65.9)	31 (22.5)	11 (8.0)	0 (0.0)	101 (73.2)	27 (19.6)	6 (4.4)	0 (0.0)
Other	34 (24.6)	33 (23.9)	93 (67.4)	14 (10.1)	15 (10.9)	5 (3.6)	94 (68.1)	20 (14.5)	10 (7.2)	3 (2.2)

All adverse events are reported as local events. Because of the design of the study (split-face), causality of the systemic adverse events cannot be assigned.

Table 2
Duration of Adverse Events after Initial Treatment, Patient Diary

	Restylane side	Zyplast side	Restylane side				Zyplast side			
	Total reporting symptoms n (%)	Total reporting symptoms n (%)	Number of days				Number of days			
			1 n (%)	2-7 n (%)	8-13 n (%)	14+ n (%)	1 n (%)	2-7 n (%)	8-13 n (%)	14+ n (%)
Bruising	72 (52.2)	67 (48.6)	7 (5.1)	56 (40.6)	6 (4.4)	3 (2.2)	7 (5.1)	53 (38.4)	5 (3.6)	2 (1.4)
Redness	117 (84.8)	117 (84.8)	19 (13.8)	68 (49.3)	18 (13.0)	12 (8.7)	19 (13.8)	71 (51.4)	15 (10.9)	12 (8.7)
Swelling	120 (87.0)	102 (73.9)	16 (11.6)	84 (60.9)	16 (11.6)	4 (2.9)	14 (10.1)	70 (50.7)	16 (11.6)	2 (1.4)
Pain	79 (57.2)	58 (42.0)	29 (21.0)	48 (34.8)	2 (1.4)	0 (0.0)	31 (22.5)	25 (18.1)	1 (0.7)	1 (0.7)
Tenderness	107 (77.5)	89 (64.5)	21 (15.2)	78 (56.5)	6 (4.4)	2 (1.4)	27 (19.6)	54 (39.1)	6 (4.4)	2 (1.4)
Itching	42 (30.4)	33 (23.9)	11 (8.0)	25 (18.1)	6 (4.4)	0 (0.0)	8 (5.8)	22 (15.9)	3 (2.2)	0 (0.0)
Other	34 (24.6)	33 (23.9)	7 (5.1)	23 (16.7)	3 (2.2)	1 (0.7)	10 (7.2)	15 (10.9)	6 (4.4)	2 (1.4)

Table 3 contains the adverse events reported during the study on the physician case report forms.

Table 3
Adverse Events Reported in the Study from Physician Case Report Forms

Description of adverse event type (WHO preferred term)	N n = 138
INFLICTED INJURY	8
SINUSITIS	7
UPPER RESP TRACT INFECTION	6
ACNE	5
BACK PAIN	3
DEPRESSION	3
DEPRESSION AGGRAVATED	3
TOOTH DISORDER	4
BRONCHITIS	2
PNEUMONIA	2
DERMATITIS CONTACT	2
ALLERGIC REACTION*	2
ARTHRALGIA	2
OSTEOPOROSIS	2
HEADACHE	2
MIGRAINE	2
HERPES SIMPLEX	2
HYPERCHOLESTEROLEMIA	2
URINARY INCONTINENCE	2

* One case of seasonal allergy, and one reaction to make-up in the peri-orbital area

In postmarket surveillance for the product in countries outside of the U.S., presumptive bacterial infections, inflammatory adverse events, allergic adverse events, and necrosis have been reported. Reported treatments have included systemic steroids, systemic antibiotics, and intravenous administrations of medications. Additionally, inflammatory reaction to Restylane has been observed with swelling, redness, tenderness, induration and rarely acneform papules at the injection site with onset at one to several weeks after the initial treatment in previously unexposed individuals, and in less than 7 days following treatment in patients known to have been previously exposed. Average duration of this effect is 2 weeks. Medicis is conducting a post-approval study to determine the likelihood of hypersensitivity reactions for patients receiving Restylane injections.

IX. SUMMARY OF PRECLINICAL STUDIES

The following biocompatibility and toxicology tests were conducted on the subject device:

Test	Result
Pyrogenicity (Rabbits):	Did not induce fever
Bacterial Endotoxin (Gel Clot Technique):	<0.5EU/mL
Acute Tox in rabbits (20 mg/ml) 7 days (intradermal):	negative (well tolerated)
Subchron. Tox in rabbits (20 mg/ml) 14 days (intradermal)	negative (well tolerated)
Subchron. Tox in rabbits (20 mg/ml) 21 days (intradermal)	negative (well tolerated)
Cytotoxicity:	negative (No cell lysis)
Ames Test:	non-mutagenic
In Vitro chromosomal Aberration study:	not genotoxic
Mouse Bone Marrow Micronucleus study:	not genotoxic
Sensitization (Magnusson & Kligman):	negative
Muscle Implantation (4 weeks in rabbits):	well tolerated
Muscle Implantation (90 days in rabbits):	no encapsulation

Restylane passed all the biocompatibility tests. The device was shown to be non-mutagenic by Ames Test. BDDE, a component of Restylane, is a sensitizer and has also found to be a mutagen in Drosophila (*Foureman et al, Environ Mol Mutagen 1994; 23(1):51-63*). An animal study was performed by an independent laboratory (CIBA-GEIGY) to study its carcinogenicity potential of BDDE. The results of this study were included in the PMA.

In the CIBA-GEIGY study, BDDE (0.05%) in acetone was used as a topical application on CF1 mice (genetically-inbred strain). Beta propiolactone was used as positive control and acetone as negative control. It was observed that there was a statistically significant increase in the incidence of lymphoblastic lymphosarcomas in female mice and there was evidence it was dose-dependent. The sponsor notes that the number of tumors observed with BDDE was not significantly different from that of the negative control, i.e., acetone, and, therefore, BDDE is not a carcinogen except for an increase in the numbers of lymphoblastic lymphosarcomas in female mice. The method used for classification of mouse hematopoietic neoplasms in the study was outdated. Using current methods for identifying and classifying mouse hematopoietic tumors shows no difference between treatment and control animals in this study.

While the FDA agrees that the animal study did not show a relationship between BDDE and the development of lymphomas, the FDA conducted a carcinogenicity risk assessment assuming a worst-case dose of 2ppm of BBDE present in Restylane. Assuming the worst-case scenario where Restylane contains 2 ppm (i.e., sponsor's minimum detection limit) of free BDDE, and the tumorigenic dose that was obtained from the CIBA-GEIGY study, the risk assessment is calculated to be 4 in 10^5 (if Total Life Time Dose is considered) and 1 in 10^8 if Daily Dose is considered. In conclusion, even using the data from the animal study in which the tumors were erroneously separated, the calculated risk of cancer is minimal.

The preclinical testing indicated that Restylane was safe to be evaluated in clinical studies.

X. SUMMARY OF CLINICAL INVESTIGATIONS

The clinical basis for approval for this pre-marketing application is the outcome of a prospective Pivotal Clinical Study performed in the United States along with an open label extension to that study.

Pivotal Study

- ***Devices***

The investigational device used in the study was the present formulation of Restylane. Restylane was delivered during study via a 0.7 cc syringe and a 30 gauge x 1/2" needle. Maximum dose per treatment session is 1.5 ml.

The control device was a cross-linked collagen implant composed of purified bovine dermal collagen cross linked with glutaraldehyde, dispersed in phosphate buffered saline and 0.3% lidocaine. This collagen implant is indicated for the correction of contour deficiencies of soft tissue. This implant was delivered during the study via 1.0 cc syringe and fine gauge needle.

- ***Design***

Highlights

The pivotal study was a 1 to 1 randomized, prospective study conducted at 6 U.S. centers to compare Restylane and Control in a within patient control model of augmentation correction of bilateral nasal labial folds: the randomized side was treated with Restylane; the opposite side was treated with Control. Treatment was considered to be complete when optimal correction as determined by treating physician discretion (not by a pre-determined change in objective measure) was found to be sustained for 2 weeks after injection. This follow-up 2 weeks post-initial or touch-up injection began the 'Baseline' for 6, 9 and 12 month follow-up. Effectiveness was studied with 6 month follow-up from 'baseline'. Safety was studied from initial treatment and touch-up through 12 month post- 'baseline' follow-up.

Masking Plan

- Patient: partially masked
- Evaluating physician: independent and masked
- Treating physician: unmasked

Primary Objectives

The pivotal study primary objective was to evaluate the safety and effectiveness of Restylane compared to Control in patients seeking augmentation correction of bilateral nasal labial folds that met study criteria.

- Effectiveness: the primary objective was to evaluate differences in effect of Restylane and Control on the visual severity of the nasolabial folds, as assessed by an Evaluating Investigator at 6 months post-'baseline'.

Optimal correction was defined to be the best cosmetic result obtainable with 2 injectable implants as determined by the evaluating physician; a specific objective score or goal for optimal correction was not defined. The evaluation parameter was the Wrinkle Severity Rating Scale (SRS) Score:

1. Absent: no visible fold; continuous line
2. Mild: shallow but visible fold with slight indentation; minor facial feature.
3. Moderate: moderately deep fold; clear facial feature visible at normal appearance but not when stretched. Excellent correction expected.
4. Severe: very long and deep; prominent facial feature; less than 2mm visible fold when stretched.
5. Extreme: extremely deep and long folds; 2-4mm visible v-shaped fold when stretched; detrimental to appearance; unlikely to have satisfactory correction with injectable implant alone.

This scoring system was validated based upon a review of 30 non-study photos by Evaluating Investigators. Based on this photo review, an SRS change of 1 was considered to be clinically significant.

- Safety: the pivotal study primary objective was evaluation of adverse events recorded by
  - Patient Diary: intensity and duration of pain, tenderness, swelling, redness, bruising and itching for 14 days post-treatment.
  - Follow-up by the unmasked treating investigator from treatment through 12 months.

Pre-screening skin testing for sensitivity to the cross-linked collagen Control was performed. Pre-screening skin test for sensitivity to Restylane was not performed due to low suspicion of hypersensitivity. However, no anti-body titers were drawn pre-treatment to collagen or to hyaluronate. Post-treatment adverse event skin testing was planned to evaluate sensitivity to hyaluronate and collagen in case hypersensitivity reaction was suspected by the unmasked treating investigator during follow-up. Criteria with protocol details are listed in the section entitled "*Hypersensitivity Reactions*".

Secondary objectives

- SRS score assessed at 2, 4, and 6 months post-'baseline' by the evaluating investigator and by the subject.
- Number of treatment sessions needed to achieve optimal cosmesis.
- Global Aesthetic Improvement (GAI): a subjective, non-validated scale assessed at 2, 4, and 6 months by the evaluating investigator and by the subject that included the following parameters:
  - Very much improved
  - Much improved
  - Improved
  - No change
  - Worse

Study Population Criteria
Highlights:

- Non-pregnant, non-lactating adults seeking augmentation correction of bilateral nasolabial folds.
- SRS 3 or 4 at pre-treatment evaluation
- Willing to abstain during the study from exclusion procedures, e.g.: Laser or chemical re-surfacing, Botox injections, aesthetic facial surgery, concurrent facial wrinkle treatments, immuno-modulary therapy, desensitization injections to meat products.
- Without active skin disease within 6 months of study entry, known connective tissue disease or immunosuppressive therapy.
- Without any aesthetic facial therapy within 6 months of study entry.
- Without coagulopathy or known allergy / hypersensitivity or planned desensitization to device components or meat products.

Study Procedure
The pivotal study procedure consisted of 2 phases:

During the first phase, the Treatment Phase, device doses were provided as required to achieve optimal cosmetic result, within maximum limits per device (i.e., 1.5 ml per dose). Patients were re-evaluated every two weeks with touch-up if correction was sub-optimal on follow-up. The 'baseline,' i.e.: post-treatment baseline, began at the visit at which optimal correction had been maintained for 2 weeks since last treatment.

The second phase consisted of follow-up. Follow-up occurred by two schedules:

- Effectiveness: At 2, 8, 16 and 24 weeks after 'baseline'
- Safety: At 2, 8, 16, 24, 36 and 52 weeks after 'baseline'

Sample Size
Sample size determination was based on the hypothesis that three times as many Restylane treated sites would remain superior compared to control at 6 months after 'baseline'. Superiority per patient was defined as a difference of at least 1 in the SRS score in favor of one of the treatments. At any time, SRS per patient is determined in whole units of SRS as the Wrinkle SRS is an integer scale. An SRS score difference or change = 1 was considered to be clinically significant based on the validation study. Minimum enrollment, accounting for potential loss to follow-up, was statistically determined to be N = 130 patients.

- **<u>Pivotal Study Outcomes</u>**

Demographics
On the basis of this design, the study enrolled a population of predominately healthy, female, Caucasian non-smokers with minimal sun exposure. There were few men or other racial/ethnic groups; few smokers or patients with extensive sun exposure.

- Gender

Male: 9 (6.6%)
Female: 128 (93.4%)

- Ethnicity

Caucasian: 122 (89.0%)
Black: 2 (1.5%)
Asian: 2 (1.5%)
Hispanic: 11 (8.0%)

- Tobacco use

Non-smoking: 118 (86.1%)
Smokers: 19 (13.9%)

- Sun Exposure

None: 83 (60.6%)
Natural Sun: 52 (38.0%)
Artificial: 2 (1.5%)

A total of 48 patients (35.0%) had not had any previous facial aesthetic procedures; data was missing for 6 patients; 83 patients (60.6%) had had prior facial aesthetic procedures.

- Collagen injection 59 (43.1%)
- Botulinum toxin injection 32 (23.4%)
- Face-lift 16 (11.7%)
- Laser Resurfacing 15 (11%)
- Chemical resurfacing 12 (8.8%)
- Autologous fat transplant 5 (3.6%)
- Other 23 (16.8%)

Patient Disposition

Number of Subjects presenting at each follow-up time point:

- Pre-treatment 138
- 'Baseline'* 138
- 6 months 134**
- 9 months 125 for safety***
- 12 months 125 for safety

*'Baseline' defined as the 2 week follow-up point at which optimal correction has been maintained for 2 weeks.
** 4 Patients were withdrawn/lost to follow-up before 6 months.
*** 9 Patients were withdrawn/lost to follow-up before 9 months

Evaluating Investigator & Patient Masking Assessment

Evaluating investigator & patient masking assessment found that the incidence of correct guess as to treatment, for both the evaluating investigator and patients, increased during the study from approximately 60% correct guess at baseline to 70% correct guess at 6

month follow-up. Masking was found to vary significantly by center. An incidence of correct guess greater than 50% is considered to suggest incomplete masking. Therefore study masking was incomplete from baseline and progressively less effective during the trial.

		Evaluating Investigator	Patient
Baseline	Correct	***88 (64.2%)***	***82 (59.8%)***
	Not correct	47 (34.3%)	46 (33.6%)
	Total reporting	135 (98.5%)	128 (93.4%)
Month 2	Correct	***91 (66.4%)***	***82 (59.8%)***
	Not correct	38 (27.7%)	41 (29.9%)
	Total reporting	129 (94.2%)	123 (89.8%)
Month 6	Correct	***96 (70.1%)***	***93 (67.9%)***
	Not correct	37 (27.0%)	38 (27.7%)
	Total reporting	133 (97.1%)	131 (95.6%)

Primary Effectiveness

Comparative SRS per patient at 6 months as determined by the evaluating investigator:

	N = 137
Restylane lower (better) than Control:	80
Restylane equal to Control:	44
Restylane higher (worse) than Control:	13

With both treatments, Restylane and Control, a mean 1.5 unit improvement of SRS was made from pre-treatment to establish optimal correction: post-treatment 'baseline' or month 0.

Mean SRS Score By evaluating investigator:

	N	Restylane	Control	Absolute Difference*
Pre-treatment	138	3.29	3.31	0.02
Baseline	137	1.80	1.79	0.01
6 months	134	2.36	2.94	0.58

*between Restylane and Control

Data demonstrate that while there was essentially no difference between Restylane and Control treated cohort sides at pre-treatment (0.02 Units SRS) and baseline after treatment (0.01 Units SRS), for the cohort of 134 patients, there was a difference of 0.58 units of SRS at 6 months.

Secondary Objectives

- Comparative SRS per patient at 6 months as determined by patients

N = 137

Restylane greater (worse) than Control:	8
Restylane lower (better) than Control:	76
Restylane equal to Control:	53

- Mean SRS score by patients

	N	Restylane	Control	Absolute Difference
Pre-treatment	138	3.33	3.37	0.04
Baseline	138	1.96	1.97	0.01
6 months	134	2.44	3.01	0.57

- Global Aesthetic Improvement by evaluating investigator

Follow-up:	0 month	2 month	4 month	6 month
N	134	136	137	137
%Restylane > Control	3.6	38.7	56.9	62
%Restylane = Control	89	52.6	34.3	29.9
%Restylane < Control	5.1	8	8.8	8

By Patient Evaluation

Follow-up:	0 month	2 month	4 month	6 month
N	133	136	137	137
%Restylane > Control	11.7	34.3	43.1	55.5
%Restylane = Control	75.9	55.5	47.4	36.5
%Restylane < Control	9.5	9.5	9.5	8

Report of the global aesthetic improvement score favoring Restylane increased over time following treatment. This trend was similar for data by evaluating investigators and patients.

- Number of treatment sessions to achieve optimal cosmesis was evaluated.

For both Restylane and Control, optimal cosmesis required 1 to 3 treatments.

Optimal Cosmesis with initial treatment alone:

- Restylane: n = 89 (65.0%)
- Control: n = 85 (62.0%)

Optimal Cosmesis requiring 3 treatments:

- Restylane: n = 7 (5.1%)
- Control: n = 3 (2.2%)

Overall, no statistically significant different numbers of treatments were required to achieve Optimal Cosmesis with Restylane or Control.

Safety
The adverse events observed in the study are included in detail in Section VIII: Potential Adverse Effects of the Device to Health.

Hypersensitivity: No hypersensitivity reactions were observed. Clinical trials have not evaluated anti-body titers before or after treatment with Restylane to allow correlation of symptoms with immune response and to objectively characterize the symptom profile associated with immune response to Restylane. The overlap of symptom profiles for Restylane hypersensitivity and injection site reactions, and lack of correlation of symptoms with anti-body titers, may have confounded diagnosis of hypersensitivity reaction to the investigational device during the pivotal trial.

X. CONCLUSIONS DRAWN FROM THE STUDIES

Based on the live investigator scores of wrinkle severity, and the global subjective assessments by the investigator and patient, effectiveness has been shown for the device. Safety has been demonstrated by the lack of severe adverse events, and by the short duration of the events observed.

Therefore, it is reasonable to conclude that 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.

XI. SKIN TYPE AND GENDER BIAS

The majority of patients enrolled in the pivotal clinical study were Caucasian (89%), who most commonly represent Fitzpatrick skin types 1 – 3. Minority populations, who more commonly represent Fitzpatrick skin types IV – VI comprised 11% of the study group. This proportion may not be reflective of the general U.S. population that may seek treatment with Restylane.

Women made up a majority of the patients in the U.S. trial (93.1%). Gender was represented as may be expected in the US market.

XII. PANEL RECOMMENDATION

This PMA was referred to the General and Plastic Surgery Panel and FDA advisory panel for review and recommendation on November 21, 2003. The panel recommended that the PMA be Approvable with Conditions. The panel recommended the following conditions:

- The sponsor should conduct a postapproval study to collect safety and effectiveness data on persons of color.
- The sponsor should remove all superiority language from the labeling.
- A statement should be placed on the labeling stating "Limited controlled clinical study data are available regarding the use of Restylane in patients with skin types V and VI on the Fitzpatrick scale and people of color."

- The sponsor should provide confirmation of physician education prior to use of the device.

XIII. CDRH DECISION

CDRH agreed with and accepted all of the Panel's recommendations with slight modifications, as follows:

- The sponsor will conduct a post-approval study on persons with Fitzpatrick skin types V and VI. The FDA believes that this range of skin types would encompass persons of color.
- The sponsor will conduct a post-approval study to assess the likelihood of hypersensitivity reactions due to injection of Restylane.
- The labeling does not include statements or claims that imply that Restylane is superior to the control device.
- To emphasize the lack of data in patients with Fitzpatrick skin types V and VI, the following precaution has been added to the labeling, "The safety of Restylane in patients with increased susceptibility to keloid formation and hypertrophic scarring has not been studied. Restylane should not be used in patients with known susceptibility to keloid formation or hypertrophic scarring."
- The sponsor has developed an educational DVD that will be provided to the physicians prior to the procedure to address the Panel's physician education recommendation.

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

The applicant's manufacturing facility was inspected on June 14, 2003, and was found to be in compliance with the Quality System Regulation (21 CFR 820).

FDA issued an approval order on December 12, 2003.

XIV. APPROVAL SPECIFICATIONS

Directions for Use: See product labeling.

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

Postapproval Requirement and Restrictions: See the approval order.