



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Sanofi Aventis U.S. LLC
% Ms. Judith R. Plon
Senior Director, Internal Medicine
Regulatory R&D Portfolio
9 Great Valley Parkway
Malvern, Pennsylvania 19355

JUL 28 2009

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

Re: P030050/S2
SCULPTRA Aesthetic
Filed: July 28, 2006
Amended: October 30, December 5 and 18, 2006, June 14 and July 27, 2007, March 20,
April 14, May 23, 2008, July 29, October 21 and 30, and December 19, 2008
and March 2 and 27, June 16, 17, 22, and 30, 2009

Dear Ms. Plon:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) supplement for SCULPTRA Aesthetic. The device is indicated for use in immune-competent people as a single regimen for correction of shallow to deep nasolabial fold contour deficiencies and other facial wrinkles in which deep dermal grid pattern (cross-hatch) injection technique is appropriate. The PMA supplement is approved. You may begin commercial distribution of the device as modified in accordance with the conditions described below and in the "Conditions of Approval" (enclosed).

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that, to ensure the safe and effective use of the device, the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii), (1) insofar as the labeling specify the requirements that apply to the training of practitioners who may use the device as approved in this order and (2) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

In addition to the periodic report (often referred to as annual report) requirements outlined in the enclosure, you have agreed to provide the following data in a separate postapproval study report for the following studies:

- A Post Approval Study to determine the visibility of SCULPTRA Aesthetic via different facial imaging techniques. Because the microparticles of SCULPTRA Aesthetic may be visible on computer tomography (CT) scans, magnetic resonance imaging (MRI), ultrasound (US) or standard, plain radiography, you will evaluate in animals the ability of these imaging

methods to detect the product and the potential inflammation occurring during device resorption. This study will monitor the device and surrounding tissue in 10 rats during a 90 day period after implantation. On completion, the study results will be submitted in a PMA supplement so that they can be presented in the product label.

- A 5-year post approval study (PAS) to assess the postmarket safety of SCULPTRA Aesthetic in immune-competent subjects when used as a single regimen for correction of shallow to deep nasolabial fold contour deficiencies and other facial wrinkles in which deep dermal grid pattern (cross-hatch) injection technique is appropriate. This corresponds to Wrinkle Assessment Scores (WAS) of 2 to 4. A single regimen consists of up to 4 sessions with 3 week intervals.

Specific objectives of this study are: (1) to determine the incidence, severity, duration, and time to onset of hypertrophic scarring, keloid formation and other changes in skin pigmentation in persons of color (Fitzpatrick skin types IV-VI), and to (2) determine the long term safety of SCULPTRA Aesthetic with regard to device-induced long term chronic inflammation (e.g., nodules, papules, granulomas, skin necrosis, hypersensitivity, and other injection site reactions).

This post-approval study will be a prospective, open-label, multi-center study conducted in the United States. You have agreed to enroll 863 SCULPTRA Aesthetic naïve subjects (including at least 22 with Fitzpatrick skin type IV and 122 with Fitzpatrick skin type V-VI) who meet the eligibility criteria described in the labeling and follow them for 5 years in order to have a total of 604 evaluable subjects with 5 year follow-up data (including at least 15 with Fitzpatrick skin type IV and 85 with Fitzpatrick skin type V-VI). Following the initial treatment regimen of the nasolabial folds, subjects' safety will be evaluated at Week 3; Months 3, 6, 9, 13 and then at Years 2, 3, 4, and 5. Subject assessment of effectiveness will be evaluated at Months 6, 13 and then at Years 2, 3, 4 and 5.

The co-primary endpoints of the PAS are: (1) The 5-year incidence rate of any nodule and/or papule at SCULPTRA Aesthetic injection site (defined as nasolabial fold injection site and/or other facial wrinkles for which grid pattern (cross-hatch) injection technique is appropriate); and (2) The 5-year incidence rate of chronic inflammation adverse events (AEs) other than nodule or papule at SCULPTRA Aesthetic injection site (as defined above). Chronic inflammation includes granulomas, skin necrosis, hypersensitivity reactions, hypertrophic scarring, keloid formation, changes in the skin pigmentation, and unexpected change in wrinkle contour. The secondary endpoints are the 2-year incidence rate of nodules, papules, any of the above chronic inflammation AE at SCULPTRA Aesthetic injection site (as defined above).

The primary hypothesis to be evaluated is that by the end of the 5 years of study follow-up the upper bound of the one-sided 95% confidence interval for the percentage of subjects (with Fitzpatrick skin types I-VI) with any injection site nodule or papule AE is less than 21%; and

the upper bound of the one-sided 95% confidence interval for the percentage of subjects with Fitzpatrick skin types I-VI) with any injection site chronic inflammation AE other than nodule or papule is less than 3%. In addition, you have also agreed to perform formal hypothesis testing for the year 2 endpoint (i.e., upper bound of the one-sided 95% confidence interval for the percentage of subjects with any injection site nodule or papule AE is less than 21%, and the upper bound of the one-sided 95% confidence interval for the percentage of subjects with any injection site chronic inflammation AE other than nodule or papule is less than 3%). The primary and secondary hypotheses will be tested for significance at the one-sided significance level of 5%, using an exact test.

Data will be collected on baseline (pre-treatment) patient demographic characteristics and device use for treatment (e.g., volume of device, number of injections), all AEs, will be collected and summarized by the number of subjects reporting adverse events, system organ class, preferred term, time of onset, severity of event, duration of event (timing relative to last injection), medical interventions required to resolve / treat such adverse outcomes, relationship to device or procedure, and different anatomic sites that the device was injected.

The assessment of other WAS 2-4 facial wrinkles for which grid pattern (cross-hatch) technique is considered appropriate will be conducted at baseline using a validated photo-numeric scale.

You have also agreed to make every reasonable effort to limit the cumulative loss-to-follow-up to less than 30% at the 5 year follow-up (with an average yearly loss <7%). If the follow-up rate is unacceptably low during the 5 year follow-up, FDA will consider other regulatory options to limit loss-to-follow-up, including requiring you to recruit more subjects.

Descriptive statistics showing the incidence of any injection site nodule or papule AEs, other chronic inflammations AEs and acute inflammatory AEs will be evaluated with the exact 95% confidence intervals for all subjects, for subjects with Fitzpatrick skin types I-III, for subjects with Fitzpatrick skin types IV-VI, for subjects with concomitant facial fillers, and for subjects without concomitant facial fillers, respectively. The percentages of subjects with each individual injection site chronic inflammation AE will be evaluated.

Every six months for the first two years and then annually until the study is completed you are to submit a progress report to the FDA that includes, but is not limited to, the status of site enrollment, the status of patient enrollment, the status of patient follow-up, and other milestones and an explanation for a delay, if any in meeting these goals, and the safety and effectiveness data collected during that reporting period.

You must also update your patient and physician labeling (via PMA supplement) to reflect the results of the post-approval study 2-year and 5-year findings, as soon as these data are available, as well as any other time point deemed necessary by FDA if significant new information from the study becomes available.

Page 4 – Ms. Judith R. Plon

Please remember that you must submit a full post-approval study protocol for each of the required studies in a separate PMA Supplement and reach agreement with OSB on the protocols within 30 days after the approval order is issued to address the remaining issues of the PAS identified in the FDA comments sent to you via email on July 2, 2009. Your new PMA supplement should be submitted in triplicate to the address below and reference the PMA number above to facilitate processing.

FDA intends to act on and respond to an applicant's protocol submission within 60 calendar days of receipt.

CDRH does not evaluate information related to contract liability warranties, however you should be aware that any such warranty statements must be truthful, accurate, and not misleading, and must be consistent with applicable Federal and State laws.

CDRH will notify the public of its decision to approve your PMA by making available a summary of the safety and effectiveness data upon which the approval is based. The information can be found on the FDA CDRH Internet HomePage located at <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/PMAApprovals/default.htm>. Written requests for this information can also be made to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the Federal Food, Drug, and Cosmetic Act (the act).

Failure to comply with any postapproval requirement constitutes a ground for withdrawal of approval of a PMA. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling affected by this supplement in final printed form. The labeling will not routinely be reviewed by FDA staff when PMA supplement applicants include with their submission of the final printed labeling a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment.

Page 5 – Ms. Judith R. Plon

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions concerning this approval order, please contact Charles N. Durfor, Ph.D. at (301) 796-5650.

Sincerely yours,



Mark N. Melkerson
Director
Division of Surgical, Orthopedic
and Restorative Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

Last Modified: 6-5-09

CONDITIONS OF APPROVAL

PREMARKET APPROVAL APPLICATION (PMA) SUPPLEMENT. Before making any change affecting the safety or effectiveness of the device, submit a PMA supplement for review and approval by FDA unless the change is of a type for which a "Special PMA Supplement-Changes Being Effectuated" is permitted under 21 CFR 814.39(d) or an alternate submission is permitted in accordance with 21 CFR 814.39(e) or (f). A PMA supplement or alternate submission shall comply with applicable requirements under 21 CFR 814.39 of the final rule for Premarket Approval of Medical Devices.

All situations that require a PMA supplement cannot be briefly summarized; therefore, please consult the PMA regulation for further guidance. The guidance provided below is only for several key instances.

A PMA supplement must be submitted when unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification.

A PMA supplement must be submitted if the device is to be modified and the modified device should be subjected to animal or laboratory or clinical testing designed to determine if the modified device remains safe and effective.

A "Special PMA Supplement - Changes Being Effectuated" is limited to the labeling, quality control and manufacturing process changes specified under 21 CFR 814.39(d)(2). It allows for the addition of, but not the replacement of previously approved, quality control specifications and test methods. These changes may be implemented before FDA approval upon acknowledgment by FDA that the submission is being processed as a "Special PMA Supplement - Changes Being Effectuated." This procedure is not applicable to changes in device design, composition, specifications, circuitry, software or energy source.

Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of a PMA supplement before implementation of the change and include the use of a 30-day PMA supplement or annual postapproval report (see below). FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence with the applicant that the alternate submission is permitted for the change. Before such can occur, FDA and the PMA applicant(s) involved must agree upon any needed testing protocol, test results, reporting format, information to be reported, and the alternate submission to be used.

Alternate submissions permitted under 21 CFR 814.39(f) for manufacturing process changes include the use of a 30-day Notice. The manufacturer may distribute the device 30 days after the date on which the FDA receives the 30-day Notice, unless the FDA notifies the applicant within 30 days from receipt of the notice that the notice is not adequate.

POSTAPPROVAL REPORTS. Continued approval of this PMA is contingent upon the submission of postapproval reports required under 21 CFR 814.84 at intervals of 1 year from the date of approval of the original PMA. Postapproval reports for supplements approved under the original PMA, if applicable, are to be included in the next and subsequent annual reports for the original PMA unless specified otherwise in the approval order for the PMA supplement. Two copies identified as "Annual Report" and bearing the applicable PMA reference number are to be submitted to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. The postapproval report shall indicate the beginning and ending date of the period covered by the report and shall include the following information required by 21 CFR 814.84:

1. Identification of changes described in 21 CFR 814.39(a) and changes required to be reported to FDA under 21 CFR 814.39(b).
2. Bibliography and summary of the following information not previously submitted as part of the PMA and that is known to or reasonably should be known to the applicant:
 - a. unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device or related devices ("related" devices include devices which are the same or substantially similar to the applicant's device); and
 - b. reports in the scientific literature concerning the device.

If, after reviewing the bibliography and summary, FDA concludes that agency review of one or more of the above reports is required, the applicant shall submit two copies of each identified report when so notified by FDA.

ADVERSE REACTION AND DEVICE DEFECT REPORTING. As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and effectiveness of the device, the applicant shall submit 3 copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850 within 10 days after the applicant receives or has knowledge of information concerning:

1. A mix-up of the device or its labeling with another article.
2. Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and:
 - a. has not been addressed by the device's labeling; or
 - b. has been addressed by the device's labeling but is occurring with unexpected severity or frequency.

3. Any significant chemical, physical or other change or deterioration in the device, or any failure of the device to meet the specifications established in the approved PMA that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the applicant's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the applicant. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the applicant shall be included in the Annual Report described under "Postapproval Reports" above unless specified otherwise in the conditions of approval to this PMA. This postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the applicant when determined by FDA to be necessary to provide continued reasonable assurance of the safety and effectiveness of the device for its intended use.

REPORTING UNDER THE MEDICAL DEVICE REPORTING (MDR) REGULATION. In accordance with the current Medical Device Reporting (MDR) regulation, 21 CFR 803.50 and 21 CFR 803.52, you are required to report adverse events for this device within the reporting time frames specified in the regulation. Manufacturers of medical devices, including in vitro diagnostic devices, are required to report to FDA whenever the manufacturer receives or otherwise becomes aware of information, from any source, that reasonably suggests that one of its marketed devices:

1. May have caused or contributed to a death or serious injury; or
2. Has malfunctioned and such device or similar device marketed by the manufacturer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Additional information on MDR, including how, when, and where to report, is available at <http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm>