DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center – WO66-G609
Silver Spring, MD 20993-0002

June 4, 2015

Merz North America
Ms. Laura Granitz
Director of Regulatory Affairs
4133 Courtney Road, Suite 10
Franksville, Wisconsin 53126

Re: P050052/S049
Radiesse® Injectable Implant
Filed: January 22, 2014
Amended: October 17, 2014, April 27, 2015 and April 28, 2015
Procode: PKY, LMH

Dear Ms. Granitz:

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 the Radiesse® Injectable Implant. This device is indicated for hand augmentation to correct volume loss in the dorsum of the hands. We are pleased to inform you that the PMA supplement is approved. You may begin commercial distribution of the device as modified in accordance with the conditions of approval described below.

The sale and distribution of this device are restricted to prescription use in accordance with 21 CFR 801.109 and under section 515(d)(1)(B)(ii) of the Federal Food, Drug, and Cosmetic Act (the act). FDA has determined that this restriction on sale and distribution is necessary to provide reasonable assurance of the safety and effectiveness of the device. Your device is therefore a restricted device subject to the requirements in sections 502(q) and (r) of the act, in addition to the many other FDA requirements governing the manufacture, distribution, and marketing of devices.

Expiration dating for this device has been established and approved at two years.

Continued approval of this PMA is contingent upon the submission of periodic reports, required under 21 CFR 814.84, at intervals of one year (unless otherwise specified) from the date of approval of the original PMA. Two copies of this report, identified as "Annual Report" and bearing the applicable PMA reference number, should be submitted to the address below. The Annual Report should indicate the beginning and ending date of the period covered by the report and should include the information required by 21 CFR 814.84. This is a reminder that as of September 24, 2014, class III devices are subject to certain provisions of the final UDI rule. These provisions include the requirement to provide a UDI on the device label and packages (21 CFR 801.20), format dates on the device label in accordance with 21 CFR 801.18, and submit data to the Global Unique Device Identification Database (GUDID) (21 CFR 830 Subpart E).

Additionally, 21 CFR 814.84 (b)(4) requires PMA annual reports submitted after September 24, 2014, to identify each device identifier currently in use for the subject device, and the device identifiers for devices that have been discontinued since the previous periodic report. It is not necessary to identify any device identifier discontinued prior to December 23, 2013. For more information on these requirements, please see the UDI website, http://www.fda.gov/udi.

In addition to the above, and in order to provide continued reasonable assurance of the safety and effectiveness of the device, the Annual Report must include, separately for each model number (if applicable), the number of devices sold and distributed during the reporting period, including those distributed to distributors. The distribution data will serve as a denominator and provide necessary context for FDA to ascertain the frequency and prevalence of adverse events, as FDA evaluates the continued safety and effectiveness of the device.

In addition to the Annual Report requirements, you must provide the following data in post-approval study (PAS) reports for each PAS listed below. You are asked to submit separate PAS Progress Reports every six months until the end of the second year and annually thereafter. Two (2) copies of each report, identified as an "OSB Lead PMA Post-Approval Study Report" in accordance with how the study is identified below and bearing the applicable PMA reference number, should be submitted to the address below.

1. OSB Lead PMA Post-Approval Study- Radiesse Radiological Evaluation Study: This is a prospective, open-label, single-site, descriptive study, designed to evaluate whether Radiesse interferes with radiological assessment by obscuring the bones of the hand. Twenty newly enrolled subjects with MHGS grade 2, 3, and 4 at baseline (10 subjects with MHGS 4 and 10 subjects with MHGS 2 and 3) will be treated with Radiesse in the dorsum of the hands and have the opportunity to receive up to 3 repeat treatments over 2 years of follow-up.

   X-rays of the hands will be taken in all study participants at the following time points: baseline (before initial treatment) and at 1- and 6-months. In addition, 12-month x-rays will be taken in subjects whose bones were not visible on the 6-month x-ray. To evaluate the appearance of cumulative injections over time, 24-month x-rays will be taken in all subjects who received 4 Radiesse treatments during the 2-year study. Each digital radiographic image will be assessed by two blinded, licensed radiologists to determine whether the bones are visible on x-ray.

   Safety endpoints include adverse events reported by treating physicians and by subjects and hand function assessments based on hand function testing and the Michigan Hand Questionnaire. Effectiveness endpoints include MHGS ratings by a masked evaluator and subject-reported GAIS score. After initial treatment, all subjects will be seen at in-clinic follow-up visits at 1-, 6-, 12-, and 24-months. In addition, pre- and post-safety evaluations will be performed for each repeat treatment on the same day of injection.

2. OSB Lead PMA Post-Approval Study- Radiesse New Enrollment Study: This is a prospective, multi-center, open-label study, designed to evaluate the safety and effectiveness of Radiesse treatment in MHGS grade 4 subjects. In addition, this study will provide safety data after multiple repeat treatments. A total of 250 subjects with MHGS grades 2, 3 and 4 at

baseline (at least 50% MHGS 4) will be enrolled in at least 5 sites and maximum of 12 sites in the U.S. Study participants will receive an initial Radiesse injection in the dorsum of the hands and have the opportunity to receive up to 3 repeat treatments over 2 years of follow-up. After initial treatment, all subjects will be seen at in-clinic follow-up visits at 1-, 6-, 12-, and 24-months. In addition, pre- and post-safety evaluations will be performed for each repeat treatment on the day of injection.

A non-inferiority hypothesis test will be conducted, comparing the 6-month rate of device/injection-related severe adverse events (primary study endpoint) in MHGS 4 versus MHGS 2 and 3 subjects combined, with an expected event rate of 17% and a 12% non-inferiority margin. A total of 244 subjects (n=122 in each group) at 6 months are required to ensure 80% power to conduct the hypothesis test. Based on an expected attrition rate of 5% per year, a minimum of 225 evaluable subjects are required to provide 2 years follow-up data. Safety and effectiveness data that are collected after 6 months and up to 2 years will be presented descriptively.

The effect of Radiesse injection on hand function will be evaluated with hand function testing and the Michigan Hand Questionnaire. The hand function tests will consist of the following: range of motion assessed by passive and active flexion/extension of the MCP joints; functional dexterity assessed using a 16-hole pegboard test; hand strength measured with a Jamar dynamometer (including grip strength, two-point tip pinch strength test, lateral pinch strength test, and three-jaw chuck pinch strength test); and sensation assessed by monofilament testing on the dorsum of the hands. Training of evaluators who will be conducting the hand function tests will be provided by an instructional video of a qualified physical or occupational therapist and an on-site sponsor trainer. Hand function testing will be performed in all subjects at baseline (prior to injection) and at 1-, 6-, 12-, and 24-months. In addition, pre-injection testing of hand function will be performed for each repeat treatment on the day of injection, and 1 month post-injection for repeat treatments.

For the first 10 subjects enrolled at each site (minimum of 50 subjects across all sites), hand function testing will be performed by 2 independent evaluators. These data will provide an assessment of inter- and intra-rater variability in hand function measures within and between sites.

Other safety endpoints include adverse events reported by treating physicians and by subjects. Effectiveness endpoints include MHGS ratings by a masked evaluator and subject-reported GAIS score. Hand photographs will be taken for safety and effectiveness evaluation at the following times: enrollment and 24-months (study exit) in all subjects; and at any follow-up visit in subjects who experience a serious or medically concerning adverse event.

Be advised that the failure to conduct any such study in compliance with the good clinical laboratory practices in 21 CFR part 58 (if a non-clinical study subject to part 58) or the institutional review board regulations in 21 CFR part 56 and the informed consent regulations in 21 CFR part 50 (if a clinical study involving human subjects) may be grounds for FDA withdrawal of approval of the PMA. In addition, the results from any post approval study should be included in the labeling as these data become available. Any updated labeling must be

submitted to FDA in the form of a PMA Supplement. For more information on post-approval studies, see the FDA guidance document entitled, "Procedures for Handling Post-Approval Studies Imposed by PMA Order" (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070974.htm).

Within 30 days of your receipt of this letter, you must submit a PMA supplement that includes complete protocols of your post-approval studies described above. Your PMA supplements should be clearly labeled as an "OSB Lead PMA Post-Approval Study Protocol" as noted above and submitted in triplicate to the address below. Please reference the PMA number above to facilitate processing. If there are multiple protocols being finalized after PMA approval, please submit each protocol as a separate PMA supplement.

Before making any change affecting the safety or effectiveness of the device, you must submit a PMA supplement or an alternate submission (30-day notice) in accordance with 21 CFR 814.39. All PMA supplements and alternate submissions (30-day notice) must comply with the applicable requirements in 21 CFR 814.39. For more information, please refer to the FDA guidance document entitled, "Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process" (www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089274.htm).

You are reminded that many FDA requirements govern the manufacture, distribution, and marketing of devices. For example, in accordance with the Medical Device Reporting (MDR) regulation, 21 CFR 803.50 and 21 CFR 803.52, you are required to report adverse events for this device. Manufacturers of medical devices, including in vitro diagnostic devices, are required to report to FDA no later than 30 calendar days after the day they receive or otherwise becomes aware of information, from any source, that reasonably suggests that one of their 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 www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm.

In accordance with the recall requirements specified in 21 CFR 806.10, you are required to submit a written report to FDA of any correction or removal of this device initiated by you to: (1) reduce a risk to health posed by the device; or (2) remedy a violation of the act caused by the device which may present a risk to health, with certain exceptions specified in 21 CFR 806.10(a)(2). Additional information on recalls is available at www.fda.gov/Safety/Recalls/IndustryGuidance/default.htm.

CDRH does not evaluate information related to contract liability warranties. We remind you;

however, that device labeling must be truthful and not misleading. CDRH will notify the public of its decision to approve your PMA by making available, among other information, 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 www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/PMAApprovals/default.htm. Written requests for this information can also be made to the Food and Drug Administration, Dockets Management Branch, (HFA-305), 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 submitting a petition for review under section 515(g) of the act and requesting either a hearing or review by an independent advisory committee. FDA may, for good cause, extend this 30-day filing period.

Failure to comply with any post-approval requirement constitutes a ground for withdrawal of approval of a PMA. The introduction or delivery for introduction into interstate commerce of a device that is not in compliance with its conditions of approval is a violation of law.

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 in final printed form. Final printed labeling that is identical to the labeling approved in draft form will not routinely be reviewed by FDA staff when accompanied by 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.

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

U.S. Food and Drug Administration
Center for Devices and Radiological Health
PMA Document Control Center – WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

If you have any questions concerning this approval order, please contact Diana Yoon, Ph.D. at 301-704-9277.

Sincerely yours,

William H. Maisel -S

William H. Maisel, MD, MPH
Director, Office of Device Evaluation (Acting)
Deputy Center Director for Science
Center for Devices and Radiological Health

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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June 30, 2015

Merz North America
Ms. Laura Granitz
Director of Regulatory Affairs
4133 Courtney Road, Suite 10
Franksville, Wisconsin 53126

Re: P050052/S049
Radiesse® Injectable Implant

Dear Ms. Granitz:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) completed its review of your premarket approval application (PMA) supplement and issued an approval order on June 4, 2015. We inadvertently made an error by stating, "Expiration dating for this device has been established and approved at two years." The correct expiration dating for the 0.8cc version of your device is two years, and the correct expiration dating for the 1.5cc version of your device should be 36 months. Therefore, the corrected statement regarding expiration dating is: "Expiration dating for the 0.8cc version of this device has been established and approved at two years. Expiration dating for the 1.5cc version of this device has been established and approved at 36 months."

We hope that this error has not inconvenienced you. If you have any questions about this corrective action, please contact Diana Yoon, Ph.D. at 301-796-7066.

Sincerely yours,

David Krause -S

for Binita S. Ashar, M.D., M.B.A., F.A.C.S.
Director
Division of Surgical Devices
Office of Device Evaluation
Center for Devices and
Radiological Health