Company Contact
Address

Re: Postmarket Surveillance (PS) Study PSxxxxxx
Trade Name: TRADE NAME
510(K) Number: Kxxxxxx

Dear CONTACT NAME:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) notified you by letter, dated [add date of approval order/substantial equivalence determination], that the [add trade name of 510(k) or PMA device] was cleared under [premarket notification (510(k)) Kxxxxxx].

Section 522 of the Federal Food, Drug and Cosmetic Act (the act), 21 U.S.C. 360l, authorizes FDA to require a manufacturer to conduct postmarket surveillance of a class II or class III device that meets any of the following criteria: (1) its failure would be reasonably likely to have serious adverse health consequences; (2) it is expected to have significant use in pediatric populations; (3) it is intended to be implanted in the body for more than one year; or (4) it is intended to be a life-sustaining or life-supporting device used outside a device user facility.

Your device is subject to postmarket surveillance under section 522 because it is a class III device that meets two of these criteria. Its failure would be reasonably likely to cause pain, dislocation, or device loosening, leading to revision (any secondary surgical procedure), which would meet the definition of "serious adverse health consequences" at 21 C.F.R. § 822.3(j). In addition, since it is a permanent implant, it is intended to be implanted in the body for more than one year.

When FDA orders postmarket surveillance, the manufacturer must submit a plan to conduct the surveillance. FDA will then determine whether the plan will result in the collection of useful data that can reveal unforeseen adverse events or other information necessary to protect the public health. Reports presented in published literature and to FDA indicate high ion concentrations of these metals and it is unclear if high ion concentrations lead to increased pain, adverse local tissue reactions, or revision. FDA is concerned that these high ion concentrations of cobalt and chromium may be related to increased rates of adverse events associated with this device, particularly increased pain, adverse local tissue reactions, or revision.

Accordingly, under section 522 of the act, we are ordering you to conduct a postmarket surveillance study of your device to address our questions below.

1. What are the adverse events observed in patients with Metal-on-Metal (MoM) total hip replacement (THR) systems seen within patients included in your study? What are the rates of expected (included in labeling) and unexpected adverse events with MoM THR? Do these rates vary across time since initial implant?

2. What are the baseline serum **and** whole blood levels of chromium, and serum **or** whole blood levels of cobalt in patients prior to THR? What are the patient population's average levels of chromium in serum and whole blood and cobalt in serum or whole blood for each year for

a minimum of eight years [or length of time on market] post-implant? Do these average levels increase over a minimum of the first eight years [or length of time on market] post-implant?

a. What are the reasons for revision? What are the patient population's average levels of chromium in serum and whole blood and cobalt in serum or whole blood at the time of revision? Is there a statistically significant difference in these levels among patients who have revisions compared with those who do not? Is there a difference in these levels at the time of initial THR compared with the levels at the time of revision?

b. Among patients who do not have a revision, what is the incidence of pain or functional symptoms? Is there a difference in chromium or cobalt levels among patients who have pain, functional symptoms or adverse events compared with those who do not exhibit these symptoms?

c. Among patients who do not have a revision, what is the incidence of adverse local tissue reaction as measured by patient physical examination and imaging? Is there a difference in chromium or cobalt levels among patients who have an adverse local tissue reaction compared with those who do not? What proportion of patients with an adverse local tissue reaction have a revision within one year?

d. How do differences in revisions, pain or functional symptoms, and adverse local tissue reactions vary across the time since initial implant?

3. What demographics or patient selection criteria are associated with higher metal ion concentrations? What demographics or patient selection criteria are associated with higher risk of revision?

4. What are the modes and causes of failure based on analysis of all of your reasonably available explanted retrieved devices?

Within 30 days of receipt of this order, you must submit your plan to conduct postmarket surveillance of your device to the address listed below. Your submission should clearly identify it as a postmarket surveillance plan and include the PS number referenced above.

You should send three (3) copies of your plan to:

Mary Beth Ritchey, RN, MSPH, PhD
Food and Drug Administration
10903 New Hampshire Ave
WO66-4104
Silver Spring, MD 20993-0002

To address the issues cited in questions 1-3 above, FDA recommends a cross-sectional study design which captures patients with or without revision to their original MoM THR at time periods between initial implant and 8 years after initial implant. FDA recommends contacting patients from multiple sites over a 3-6 month period and collection of information via one-time clinical visit. FDA recommends assessment of pain or functional symptoms beginning at 3 months post-initial implantation. In addition to other clinical assessments, FDA recommends

evaluation of cardiac, neurological, and immunosuppressive events, occupational and environmental exposures, history of allergy to metal ions, activity level, vitamin supplements, use of other medical implants, separate pain and functional scores from Harris Hip Score, and occurrence of severe pain leading to hospitalization/physician consult. FDA recommends assessment of imaging to include findings of loosening, migration, subsidence, resorption, presence of osteolysis, and soft tissue masses.

To address the issue cited in item 4 above, FDA recommends that you: (1) incorporate a failure analysis study within your clinical study protocol to evaluate all reasonably available explants from the clinical study subjects and (2) establish a separate, broader failure analysis study to evaluate all of your reasonably available commercially marketed devices that have been explanted from patients not participating in the clinical study. The failure analysis should include, but not be limited to, analysis of taper/trunnion involvement. Alternatively, you may choose to have one separate failure analysis study that captures both the clinical study subjects and the other patients implanted with your marketed device. In addition, when determining which clinical and demographic data may be associated with device failure, you should not only analyze the information from subjects whose devices were explanted, but also analyze and compare this information to that from subjects without explanted devices.

FDA recognizes the limitations and variations of current blood tests for chromium and cobalt. Study designs should address these limitations by including a description of the test or tests that will be used, data demonstrating the analytical validation for the tests including validation of the collection devices and pre-test processing, identification of calibration and quality control with a recognized reference material and the identification of the High complexity CLIA-certified laboratory that will be used. If more than one CLIA-certified laboratory is used, data may not be able to be pooled across laboratories.

Failure of a manufacturer to meet its obligations under section 522 is a prohibited act under section 301(q)(1)(C) of the act, 21 U.S.C. 331(q)(1)(C). Further, under section 502(t)(3) of the act, 21 U.S.C. 352(t)(3), a device is misbranded if there is a failure or refusal to comply with any requirement under section 522 of the act. Please note that violations of sections 301(q)(1)(C) or 502(t)(3) may lead to regulatory actions including seizure of your product, injunction, prosecution, or civil money penalties.

Sincerely yours,

Thomas Gross, MD, MPH
Acting Director
Office of Surveillance and Biometrics
Center for Devices and Radiological Health
Food and Drug Administration

cc: Mary Beth Ritchey
Cara Krulewitch
Deepa Gavini
Elizabeth Frank
Jonette Foy
Matthew Krueger
Eric Horowitz
Steven Wood
Barbara Buch
Danica Marinac-Dabic
Aron Yustein
Tom Gross
Philip Desjardins
Nancy Stade