DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

DePuy Orthopaedics, Inc.
% Jordan Lee, Ph.D.
Regulatory Affairs Project Manager
700 Orthopaedic Drive
Warsaw, Indiana 46581

AUG 13 2009

Re: P070018
DePuy ASR (Articular Surface Replacement) Hip System
Filed: July 13, 2007
Amended: July 16, 2007; July 16, 2007; September 11, 2007; September 21, 2007; October 2, 2007; November 5, 2007; May 9, 2008; June 6, 2008; June 30, 2008; March 24, 2009

Dear Dr. Lee:

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).

We regret to inform you that CDRH has determined that your PMA is not approvable based on the requirements of 21 CFR 814.44(f), and, where practical, FDA must identify measures necessary to make the PMA approvable. Accordingly, to place your PMA in approvable form, you must amend it to include the following:

Based on our review of the data submitted in the original PMA, as well as the data submitted in response to our letter dated November 14, 2007, we continue to believe the information you have supplied from the following:

- an IDE (G040030) that was not completed as per its originally approved protocol;
- a postmarket foreign study (b) (4); and
- some additional control data from a historical IDE study (G960262)

and the individual and combined analyses of the data from these sources are inadequate to allow for an evaluation of safety and effectiveness of your device. As a result, the Agency believes that it is necessary to provide a new clinical dataset to support the determination of a reasonable assurance of safety and effectiveness.

Our decision is based upon the following deficiencies:

1. In our letter dated November 14, 2007, we asked that you follow all enrolled G040030 IDE patients to 24 months prior to responding to the issues identified in the letter. You have completed follow up on the majority of G040030 ASR™ investigational patients, but you have not completed the follow up of control patients specified by the approved IDE protocol.

2. The PMA submission attempted to combine the available investigational and control device data of the IDE with additional investigational device data from a prospective, postmarket foreign study [redacted] (b) (4) and historical control data from another IDE study (G960262). In doing so, you believed that you had supplied a sufficient number of investigational and control patients to compare the success rate of the primary composite outcome. However, as discussed in the November 14, 2007 letter, there are several reasons why the pooling of the data is not appropriate including, but not limited to, the following: selection bias due to the selection of the proposed control data from a previously closed IDE; differences in patient demographics and patient outcomes; and the *post hoc* nature of the statistical and comparative analyses without adequate statistical corrections.

3. In addition, because of the differences in study design and data collection between the G040030 IDE study and the supplemental [redacted] (b) (4) study, there appear to be insufficient data to comprehensively analyze the device in terms of expected frequency and time course of adverse events related to the characteristics of the device and its surgical installation, or to identify the surgical technique and patient selection criteria that may predispose an individual to failure.

4. You reported conducting multiple analyses which did not yield a statistically significant result. However, you then reported that non-inferiority was achieved in one analysis in which you selectively disqualified initial radiographic failures by redefining radiographic outcomes and excluded an investigational site with a high failure rate. This *post hoc* analysis was done without an adjustment for covariates or consideration of multiplicity and raises questions of scientific validity of the approach. As such, FDA finds that this *post hoc* data analysis is insufficient to establish the safety and efficacy of this device.

5. After you performed an unplanned, interim analysis of IDE results, and selected historical control data with characteristics and implants that were different than the approved concurrent control cohort of the IDE, a *post hoc* analysis still failed to meet the prospectively defined composite primary endpoint in order to demonstrate safety and efficacy of your device.

FDA recommends you provide a new clinical dataset to support the potential determination of a reasonable assurance of safety and effectiveness of the DePuy ASR™ Hip System.

In addition to the deficiencies listed above leading to the not approvable decision, you should also address the deficiencies listed below in order to put your submission in approvable form:

1. In your PMA, you refer to several other post-marketing studies of the ASR™ conducted outside of the United States, and you report considerable worldwide distribution of the ASR™ Hip System. Please provide all reasonably known and obtainable information to support the safety and effectiveness of the ASR™. If you have access to available additional clinical, radiographic, revision, and adverse event data from both the investigational and control devices to submit for consideration, please be aware of the following issues with the incorporation of supplemental data from (b)(4) and G960262, as well as the incorporation of additional data analyses, which should be taken into consideration for any future submissions:

   a. A comprehensive understanding of patient, device, and surgical technique factors in a clinical study which may have contributed to poor outcomes is important and allows you to adequately label the device in a manner that will help to ensure its safe and effective use. A high rate of failures was observed in IDE G040030 at (b)(4), and you determined that it was possible that the surgeon may have used another manufacturer's instrumentation in some of the ASR™ procedures. You conclude, "Since the surgeon was unable to prove which subjects had been implanted with all DePuy ASR™ instrumentation, all of the subjects enrolled at (b)(4) will be excluded." Given your experiences with (b)(4) you have included a labeling warning against use of the ASR™ Hip System with any other manufacturer's instruments and components, and have modified your surgical training program. This is appropriate. However, the realm of what occurs during a clinical study with an experienced investigator, under controlled conditions, is likely narrower than the expected occurrences when your device is marketed more widely under uncontrolled conditions. Moreover, you do not appear to have direct evidence that the labeling warning and training program completely mitigate this risk. Use of incorrect instrumentation or technique is a plausible cause for the femoral neck fracture rate, but other factors may have been involved. Therefore, it was not appropriate for you to exclude any site (e.g., IDE (b)(4) from your primary analysis as per your originally approved analysis plan and future studies should analyze all sites involved.

   b. In a *post hoc* analysis, you claim to have demonstrated non-inferiority when doing an unadjusted analysis on the combined data using the Gruen and Boldt criteria and excluding (b)(4). This claim is based on a one-sided confidence interval using an alpha level of 0.05. While a one-sided test at the 0.05 level was agreed upon at the original IDE protocol stage, we believe that the Type I error rate has been inflated by doing an unplanned interim analysis and also by analyzing the data in many different ways to find a significant result. Any adjustment for multiplicity would decrease the alpha level, and if an alpha level below 0.04 is used for this one-sided test, then you would be unable to

demonstrate non-inferiority. Please adjust for multiplicity appropriately in any future *post hoc* analyses.

c. You have shown through propensity score analysis and analysis of baseline demographics that the investigational and control groups were significantly different. Although you adjusted for the differences between studies by using covariates in your analyses, you claimed that the unadjusted results were more meaningful. You justified your claim with the following statement, (b) (4) The Agency does not agree with this reasoning for use of unadjusted results. (b) (4) Please in the future use an adjusted analysis as the primary analysis or provide adequate justification for not doing so.

d. (b) (4) Clinical measures and radiographic measures are not intended to be completely redundant, but each contributes important information to the determination of a reasonable assurance of safety and effectiveness. We believe it would be burdensome for an applicant to attempt to establish the expected service life of an arthroplasty device prior to marketing, as these devices are generally permanent implants, designed for considerable longevity, and an extensive duration of follow up would be necessary in

order to follow the majority of patients until failure. However, the benefit of arthroplasty devices, given risks associated with their implantation and failure, is expected to extend beyond the point of primary outcome assessment (typically, 24 months). Thus, the inclusion of radiographic analysis in the 24-month primary outcome, along with the Harris Hip Score (which indicates current clinical performance), and absence of device related adverse events and revisions (which indicate prior clinical problems which had to be surmounted to achieve present performance), is of great consequence because it may provide some indication of future device performance. Such a composite endpoint has been consistently recommended by the Orthopaedic Devices Panel and successful total hip arthroplasty and hip resurfacing arthroplasty has thus been defined to incorporate both clinically and radiographically satisfactory results at 24-month follow up. In future studies, decisions about how to evaluate radiographs, what radiographic findings will constitute radiographic failure criteria, and who will perform evaluations should be made *a priori*, in order to avoid bias.

e. According to Exhibit 1-C1 Table 5F, all of the IDE subjects had a Harris Hip Deformity Subscale Score of 4. (Four was both the minimum and the maximum for both the control and investigational group.) According to Exhibit 1-C1 Table 40E, all of the Ultima control subjects had a Harris Hip Deformity Subscale Score of 0. (The minimum and maximum are both zero.) It seems unlikely that there should be such a dramatic difference between the groups. This discrepancy explains why the Harris Hip Scores are substantially lower for the Ultima control group. If this was a clerical error, please adjust the Harris Hip Scores and correct all of the tables and results accordingly. If there truly is a difference between the groups, please explain why the difference exists and justify the poolability of the data sets.

f. From its inclusion in your bibliography, there appear to be some publicly available data on the ASR™ that suggest somewhat poorer results for the device than results suggested by the data which you submitted from (b) (4) Based on this information, and on your original SSED draft, which referred to several other postmarket studies of the device outside of the United States (OUS), it is unclear how you avoided study selection bias in choosing the OUS study data which you used to supplement your G040030 IDE data. The (b) (4) study investigators were experienced surgeons who have published on their ASR™ results. It is unclear if, given their level of experience and the retrospective incorporation of the (b) (4) data into the PMA, they used an identical surgical technique to the surgical technique in G040030. If you submit new OUS data, please summarize other reasonably known ASR™ safety and effectiveness data from all of your foreign studies and please clarify why you selected a particular dataset as adjunctive.

g. You have used historical control data from G960262 in conjunction with some of the concurrent IDE control data from G040300 to form a control group. It is not clear that pooling of the two sets of control data is appropriate. The control G960262 patients

received different hip constructs than the control patients of G040030. In addition, there was (b)(4) the rate of diagnosis of avascular necrosis in the adjunctive control data relative to the control G040030 arm, and the composite success rate was almost 9% lower in G960262 control patients than in G040030 controls. It is not clear how you avoided bias in selecting this adjunctive control dataset. Historical data should not supersede the concurrent control. Please provide follow up on the remainder of your G040030 IDE control cohort or make individual comparisons to all reasonably known and obtainable control patient data sets.

h. In Tables 6 and 8 of the proposed Instructions for Use and the Summary of Safety and Effectiveness, the reported unadjusted investigational success rate using the Gruen and Boldt criterion and excluding (b)(4) is (b)(4). This success rate is not non-inferior to the corresponding control success rate, (b)(4) as you have indicated. From the electronic data and the statistical analysis section, it is believed that these tables are incorrect. There are other instances throughout Amendment 008 where there also appear to be data discrepancies and inconsistent patient accounting. Please ensure that all of the reported numbers in your submission are clear and accurate, especially those to be included in any patient or physician labeling.

2. It appears information was removed from the SSED draft derived from studies which were not reviewed in the PMA (specifically, (b)(4) and this is appropriate. However, it is unclear if reasonably known information from each of these studies is included in the bibliography. Under 21 CFR 814.20(b)(8)(ii), you should be reporting all reasonably known information relevant to the safety and effectiveness of the device, including information (both published and unpublished) derived from investigations other than those proposed to support reasonable assurance of safety and effectiveness in the application and from commercial marketing experience. Please clarify how the information which you obtained from these postmarketing studies relates to the information which you have submitted in the bibliography, and please include results for other investigations (b)(4) as well as any other studies you have conducted) if they have not been reported.

3. You have provided several abstracts with selected blood metal ion analyses from patients implanted with the ASR™ Hip System. The high concentration of metal ions observed in some of these patients is concerning. Since (b)(4) data are not part of the PMA dataset, please clarify how the characteristics of the patients, surgical technique, and methodology of the study compare to the PMA dataset. In addition, please examine the association between (b)(4) and submit patient-level data, including clinical and radiographic outcomes and adverse events/revisions/reoperations for these patients.

4. In our November 14, 2007 letter, you were asked to supply fatigue testing on the worst case femoral component, as testing was conducted on a (b)(4) component. You acknowledge

that the smallest femoral component has the smallest pin and is therefore the worst case device. However, you have not supplied testing on the worst case component. You did supply a Finite Element Analysis (FEA) of a (b)(4) component, which you state is the smallest component with the smallest feature dimensions. Note that your engineering drawings appear to show smaller components with smaller feature dimensions. Furthermore, FEA is not considered an acceptable surrogate for experimental data, as it is limited by model assumptions and it represents the theoretical behavior of the device design, not the actual behavior of the device as produced. Although you state that there is no design criteria for this pin because it is only intended to serve as a guide during implantation, if this pin contacts bone or bone cement, or if the femoral neck is fractured, it is loaded. Pin loading cannot be unilaterally avoided in device implantation. Therefore, it is important to characterize pin behavior during this worst case situation. Please conduct fatigue testing on the worst case femoral component to characterize fatigue strength of the fixation pin. Justification of the worst case size should be provided in detail. If the availability of a suitably sized bone model is a pragmatic limitation to performing the testing which you conducted for the (b)(4) component, cantilever loading may be utilized.

5. You were asked to provide evidence that the ASR™ femoral components were appropriately sterilized. Within Amendment 8, you state that, following (b)(4), you have determined that the ASR™ femoral components were covered under validations (b)(4) Although you have provided the Agency with a blank copy of (b)(4), which gives some insights into how you determine whether a separate sterilization validation is required for a particular component relative to the features of the validated master product, and you have stated that you have documented how ASR femoral components were determined to be covered under the existing validations in (b)(4), because you have not submitted (b)(4) (which does not appear to be included in (b)(4)), the sterilization validation documentation for the ASR femoral components remains incomplete. In order to provide reasonable assurance of the safety of your device, evidence of device sterility is needed. Accordingly, please submit the completed documentation which shows precisely how you concluded that the ASR™ femoral component sterility was covered under existing validations, or provide other evidence (e.g., a sterilization validation report) that supports the sterilization of the ASR™ femoral components.

6. Within Amendment 008, you have provided the documentation for the sterilization of the (b)(4) which adequately supports the sterilization validation of the ASR™ Shells which are coated by (b)(4) However, we noted that you are currently proposing that your coating be applied by (b)(4) different vendors. The documentation for the sterilization validation of the ASR™ Shells which are coated by (b)(4) does not appear to have been submitted (b)(4) Because your acetabular components are coated by (b)(4) different vendors, and the bioburden is likely different in these (b)(4) different manufacturing environments, sterilization validation data and documentation

are needed for components from each vendor. Please supply additional information about the sterilization of ASR™ acetabular components which are coated by (b)(4)

7. You have provided validation data for the packaging system of the ASR™ which appears to address the important question of whether or not the system is capable of maintaining a sterile barrier through the device's requested (b)(4) shelf life, under shipping/transit conditions. Another aspect of shelf life is that device characteristics and performance are not altered by storage conditions. Within Amendment 8, it does not appear that you have provided adequate documentation that this aspect of shelf life was addressed. While it may be reasonable to assume that the all-metal components of the DePuy ASR™ are unaltered by storage and shipping based on the testing you have already conducted, the stability of the (b)(4)-coated components raise concern. It is not clear how you determined that your coating was either unaffected by shipping and storage conditions, or that any effects were inconsequential. Further, it is unclear how moisture proof your packaging system and its seals are, or if the coated components are packaged under set environmental conditions; some (b)(4) coatings may react with moisture in the air and/or may be susceptible to effects of humidity and temperature fluctuations and mechanical damage, potentially changing surface morphology, bonding strength, and other important coating characteristics. To adequately address the requested shelf life of your system, please provide full characterization of your (b)(4) coating (from each vendor) at the end of the (b)(4) shelf life, as well as documentation of methods and test results that show the coating on the ASR™ acetabular components was intact after the transit testing that you conducted.

8. In your response to Deficiency 28, you have clarified that the average bead diameter of the (b)(4) is estimated at (b)(4) microns. This is based on theoretical expected size distributions, assuming normality, from the (b)(4) However, you have not provided appropriate characterization information which demonstrates that the actual size of the beads in the (b)(4) matches the predicted sizes of the finished coating. In addition, a complete characterization of the (b)(4) with an estimated bead diameter of (b)(4) microns is not available in (b)(4) Therefore, your device description remains incomplete. As previously recommended, please provide the complete characteristics of the subject (b)(4) on the acetabular shells as outlined in the "Guidance Document for Testing Orthopedic Implants with Modified Metallic Surfaces Apposing Bone or Bone Cement" (available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm081034.htm). Test reports should be supplied which address each of the items in the guidance, including specifically identifying the shape and size of the particles used in the (b)(4) with measured average, standard deviation, and range. In addition, please provide additional information about any properties of the (b)(4) which are modified (b)(4)

9. The DePuy ASR™ acetabular components include a [redacted] coating [redacted] In our November 14, 2007 letter, we requested an overview of the [redacted] coating, per the document ("510(k) Information needed for [redacted] Coated Orthopedic Implants") available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080224.htm, and explicitly requested that you fully describe how each supplier meets these specifications. Within Amendment 8, you responded to this request by providing your requirements for [redacted] coating. However, it is unclear if these specifications are comprehensive enough to ensure a consistent coating. (For example, your current specifications do not address the foreign phases, the solubility product, the [redacted] ratio, etc).

In addition, you have not provided adequate information to fully characterize the coating produced by each vendor's process when imposing these requirements. In many of the issues below, we request that you refer to the National Institute of Standards & Technology (NIST) Standard Reference Material [redacted] material/method. This [redacted] Standard Reference Material (SRM) is available at http://ts.nist.gov/srm. Note that all testing should be performed on final, sterilized devices and, as previously requested, characterization information should be provided for devices coated by each of your [redacted] vendors. If some of this information is specifically located in the Master Files [redacted] and [redacted] from [redacted] respectively, please provide the page numbers on which the information is located. Please provide additional information to specifically address the following issues for coatings on the ASR acetabular components from each vendor:

a. Your specification states that the phase composition shall be not less than [redacted] It is not clear from this specification what other phases may be present and in what quantity. Your specification to the vendor stipulates that the [redacted] However, there are a number of ways in which this calculation may be performed and valid measurement requires comparison to a reference material. We recommend that you calculate the [redacted]

b. You state that the total [redacted] content of the coating [redacted] should meet the specifications in [redacted] FDA needs to be assured that there are no

(b)(4) residues present in the coating. Please provide additional characterization of the coating to address this concern. In addition, please provide an explanation of the use of the historical standard (b)(4)) for the (b)(4) versus the current standard ((b)(4)), highlighting any relevant differences.

c. Please provide the (b)(4) ratio of the coating (b)(4)

d. Please report the total surface area of the (b)(4) portions of the ASR devices. For all (b)(4) coatings, in order to fully characterize your device, we request that you determine the surface area by the triple-point method of (b)(4) Please refer to the NIST Standard Reference Material (b)(4) for this method (or contact NIST for more details).

e. You have provided a summary of the (b)(4) coating characteristics in Volume 2, Book 1, pg. 2 of the original submission (which still need to be substantiated with data. See Deficiency 8 above). However, the addition of a (b)(4) coating to the (b)(4) This quantitative information is needed to provide a complete and accurate description of the (b)(4) coating. (b)(4)

f. An important characteristic of a (b)(4) coating is the solubility and the solubility product of your coating. This information does not appear to have been provided. FDA compares the solubility product of the (b)(4) coatings with the NIST Standard Reference Material (b)(4). Please provide the solubility product, (b)(4) The pH changes of the solution should also be recorded. The solubility product (b)(4) should be calculated based on (b)(4) formula. FDA recommends either using the NIST method or side-by-side comparison with the NIST 2910 Standard Reference Material.

g. The dissolution rate of your calcium phosphate coating is needed. We recommend that the dissolution tests be performed in a physiologic, simulated solution with the dissolution rate reporting the (b)(4) ions and/or the (b)(4) ions verses time (e.g., (b)(4) (b)(4).

h. Please indicate if any post-deposition processes (e.g., (b)(4) are used.

i. Please provide the (b)(4) of the (b)(4) before and after coating, including detailed molecular interpretations of the (b)(4)

j. The bonding strength between the proposed (b)(4) coating and (b)(4) is not clearly reported. Please provide bonding strength data from a sufficiently sized sample to measure the standard deviation in this parameter, and include the test protocol and methods of sample preparation.

10. Please note the following advisories:
    - You have prepared numerous tables of summary data which report the average outcome results for various study metrics, as well as printed output of statistical analyses, and you have submitted more detailed information on some of the patient failures. However, the clear interpretation of the PMA data has been thwarted by the lack of concise, line-by-line data in the submission for each patient which shows their results on all elements of the composite and conveys clearly whether or not the patient was categorized as a success, a failure, or an unevaluable outcome and for what reason(s).

    - Please be advised that until sufficient information is provided to address the deficiencies identified within this letter, our review of your product label, Instructions for Use, and Summary of Safety and Effectiveness (SSED) cannot be completed. We will have additional comments if you submit a response to this letter which provides reasonable assurance of the safety and effectiveness of your device. As such, FDA cautions that you not finalize your physician or patient labeling at this time.

The deficiencies identified above represent the issues that we believe need to be resolved. In developing the deficiencies, we carefully considered the statutory criteria as defined in Section 515 of the Federal Food, Drug, and Cosmetic Act for determining reasonable assurance of safety and effectiveness of your device. We also considered the burden that may be incurred in your attempt to respond to the deficiencies. We believe that we have considered the least burdensome approach to resolving these issues. If, however, you believe that information is being requested that is not relevant to the regulatory decision or that there is a less burdensome way to resolve the issues, you should follow the procedures outlined in the "A Suggested Approach to Resolving Least Burdensome Issues" document. It is available on our Center webpage at: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073704.pdf.

This is to advise you that an amendment including the above requested information will be considered a major amendment and may extend the FDA review period up to 180 days. As provided by 21 CFR 814.37(c), you may decline to submit a major amendment requested by FDA in which case the review period may be extended for the number of days that elapse between the date of such request and the date that FDA receives the written response declining to submit the requested amendment.

As provided by 21 CFR 814.44(f), you may amend your PMA as requested above, withdraw the PMA, or consider this letter to be a denial of approval of the PMA under 21 CFR 814.45 and request administrative review. Any request for administrative review, either through a hearing or review by an independent advisory committee, under section 515(d)(4) and 515(g) of the Federal Food, Drug, and Cosmetic Act, must be submitted in the form of a petition for reconsideration under 21 CFR 10.33 and in accordance with the general administrative procedures under 21 CFR 10.20. Any petition for reconsideration must be submitted to the Food and Drug Administration, Dockets Management Branch (HFA-305), Room 1061, 5630 Fishers Lane, Rockville, Maryland 20852, within 30 days of your receipt of this letter. After reviewing the petition, FDA will decide whether to grant or deny the petition and will publish a notice of its decision in the FEDERAL REGISTER. If FDA grants the petition, the notice will state the issues to be reviewed, the form of the review to be used, the person may participate in the review, the time and place where the review will occur, and other details.

As provided under 21 CFR 814.44(g), FDA will consider this PMA to have been voluntarily withdrawn if you fail to respond in writing within 180 days of the date of this request for a PMA amendment. You may, however, amend the PMA within the 180-day period to request an extension of time to respond. Any such request is subject to FDA approval and should justify the need for the extension and provide a reasonable estimate of when the requested information will be submitted. Please note that FDA intends to allow one extension (180 day maximum). If you do not amend the PMA within the 180-day period to (1) correct the above deficiency(ies), or (2) request an extension of time to respond and have the request approved, any amendment submitted after the 180-day period will be considered a resubmission of the PMA and will be assigned a new number. Under these circumstances, any resubmission will be given a new PMA number and will be subject to the requirements of 21 CFR 814.20.

You may amend the PMA to provide the above requested information (6 copies), voluntarily withdraw the PMA (3 copies), direct CDRH to complete processing the PMA without the submission of additional information or request an extension.

The required copies of the amended PMA should include the FDA reference number to facilitate processing for this PMA and should be submitted to the following address:

U.S. Food and Drug Administration
Center for Devices and Radiological Heath
PMA Document Mail Center – WO66-0609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

If you have any questions concerning this not approvable letter, please contact Christina Beardsley, Ph.D., at (301)796-6404.

Sincerely yours,

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