24-Hour Summary
Orthopaedic and Rehabilitation Devices Panel
Day 1 – June 27, 2012

Introduction:
The panel will discuss the current knowledge about the safety and effectiveness of Metal-on-Metal (MoM) hip arthroplasty systems. FDA convened this committee to seek expert scientific and clinical opinion on the risks and benefits of these types of devices based on available scientific data.

Professional Societies:
FDA began the day with an introduction and overview of MoM total hip systems and resurfacing systems available in the US. Paul Manner, MD, Markus Wimmer, PhD, and Young-Min Kwon, MD, PhD presented from the American Academy of Orthopaedic Surgeons (AAOS), American Association of Hip and Knee Surgeons (AAHKS), the Hip Society and the Orthopaedic Research Society (ORS). Dr. Manner presented a history of MoM hip systems with current clinical outcomes and results of the society's recent technology overview. Dr. Wimmer discussed preclinical testing, implant retrieval analysis, and tribology/tribocorrosion. He summarized the current activity and research needs identified by the American Society for Testing Materials (ASTM). Dr. Young-Min Kwon commented upon local and systemic effects, management strategies, and algorithms and further standardization of histological evaluation of periprosthetic tissues is needed.

Industry:
Industry presentations were made by Biomet, DePuy, Smith & Nephew, and Corin. Biomet discussed the design features of the Biomet MoM total hip arthroplasty (THA) system, metal ion levels, and the performance of their MoM THA system. DePuy presented registry data on the ULTAMET MoM articulation. Smith & Nephew discussed the design, surgical technique, training and patient selection for the BHR. Corin discussed their experience with the Cormet hip resurfacing device including their US clinical trial data and experience with US surgeons. All of the manufacturers emphasized MoM hip systems are not the same and each device should be evaluated on its own merit.

Open Public Hearing:
During an open public hearing seven patients presented their personal experiences with MoM hip systems. The patients had adverse tissue reactions debilitating their lives, making daily life activities unmanageable, requiring revision surgery. Many patients recommended all MoM hip systems be removed from the market. One additional patient shared her experience with a metal on polyethylene total hip replacement empathizing with the patients with MoM hip systems.

Outside of the US Regulatory Bodies and Professional Societies:

Several regulatory bodies and professional societies from outside of the US discussed their experience with MoM hip systems. The Medicines and Healthcare products Regulatory Agency (MHRA), UK, highlighted their Expert Advisory Group and the Medical Device Alerts, which include recommendations for metal ion testing, imaging and revision surgery. Dr. Skinner represented the British Hip Society and British Orthopaedic Association highlighting their recommended follow up parameters. The Therapeutic Goods Administration (TGA) from Australia indicated they have not yet made an official position statement, but they suggest looking at rising level of metal ions with imaging. The Australian Orthopedic Association discussed the decline in usage of MoM hips in Australia and their standard follow-up for each implant size. The Canadian Orthopaedic Arthroplasty Society emphasized surveillance of at-risk population is needed including females and those with poorly oriented components.

Device Mechanics and Failure Modes:

Steven Kurtz, Ph.D., and Jeremy Gilbert, Ph.D, were guest speakers. They presented on "Metal-on-Metal Hips: Device Mechanics and Failure Modes" and "Hip Implant Corrosion Mechanisms and Effects: Mechanically Assisted Corrosion, Crevices and Voltage Effects", respectively. Smith & Nephew and Corin each presented. The guest speakers discussed: femoral neck thinning and fracture of resurfacing systems; elevated wear and edge wear as failure modes of both resurfacing and THR systems; mechanically assisted corrosion; how wear and corrosion are coupled and interactive; and potential biological effects of voltage changes resulting from corrosion. The panel then had the opportunity to ask questions of the presenters. The panel then deliberated on the device failure modes of metal on metal hips. Some of the topics discussed during the deliberation were: contact patch change over time of implant; micro-separation; gender differences; corrosion; impingement; edge wear; and trunnions.

Registry Data:

Dr. Graves and Dr. Sedrakyan presented revision data from the International Consortium of Orthopedic Registries (ICOR). Dr. Ritchey of the FDA presented an overview of the revision data identified in the published literature. They presented revision rates from registries around the world with specific focus on the Australian and UK data as well as the preliminary combined data from ICOR. In addition, as data was available, revision rates were presented by time since implant, region, sex, age, and femoral head size. Biomet and Smith & Nephew presented registry data on their respective MoM hip systems.

The Panel discussed the need to account for key differences between practice of medicine and patients in the United States compared with other countries. The Panel specifically discussed the need to account for increased obesity in the US, access to implants earlier within disease progression in the US, surgeon experience and volume, and that a larger number of older patients receive metal on metal hip implants in the US. In addition, the Panel felt that continued evaluation of patients after revision is needed.

The Kaiser Permanente registry was discussed as the best source of US data currently available showing no difference in revision rates between MoM hips and other bearing surfaces, and showing a higher incidence of failure with smaller MoM THA head sizes. However, the Kaiser registry only represents a subset of products available in the US and utilizes very few large diameter heads. Panel Members also felt the Kaiser registry may not be representative of care throughout the US.

The surgeons on the Panel believe that there are several variables that are critically important, particularly after the data are stratified (allowing for evaluation of more homogeneous groups of patients), specifically:

- BMI
- Difficulty of revision procedure
- Continued follow-up after revision
- Differences by gender
- Surgeon training, preferences, and years of experience
- Available devices within each region – different devices are available (e.g. US vs OUS or within a specific managed care environment)

The Panel felt that while data from registries are different than data derived through clinical trials, registries are good sources for looking at revision surgery as an endpoint. However, the Panel noted that completeness of registries, including follow-up assessment, is needed to determine the utility of each dataset.

Summary:

During Panel deliberations there were differing opinions on whether revision of a failed MoM stemmed hip replacement or resurfacing hip replacement was more challenging. Overall, the Panel believed revision of failed a MoM hip system is likely to be more challenging than revision of a failed metal-on-polyethylene hip replacement.

At the end of the day, Panel Members shared their highlights from the day. Some Panel Members expressed there are risks and benefits to all bearing surfaces, and as a surgeon you need to be knowledgeable about how these risks and benefits apply to each patient. The Panel recognized the powerful stories from all of the patients. This led to a discussion on how patient expectations in the United States may differ from other parts of the world.

The Panel agreed there is evidence of heterogeneity of devices, as well as a heterogeneity of outcomes, making this an extremely complex issue with a multitude of variables. Differences in gender and concern for why women respond differently than men were a recurring concern throughout the discussion. The Panel felt there must be a biological aspect that has not been addressed.

Panel members raised questions on the treatment algorithm for those patients who have been treated with the MoM hip systems. The Panel recognized patients deserve the best and most transparent information available. On Day 2, the Panel will hear about soft tissue imaging, metal ion testing, and systemic and local complications, and will discuss how to advise patients considering hip replacement surgery and how to treat patients with MoM hip systems.

24-Hour Summary
Orthopaedic and Rehabilitation Devices Panel
Day 2 – June 28, 2012

Introduction:
FDA began the day with an overview of the presentations from Day 1.

Soft Tissue Imaging:
Dr. Young-Min Kwon discussed soft tissue imaging in metal on metal hip systems. He discussed the importance of soft tissue imaging for comprehensive evaluation of a patient and how imaging is only one piece of the diagnostic algorithm. Dr. Kwon also discussed the utilities and limitations of different imaging modalities. Some of the imaging modalities discussed were radiographs, CT, ultrasound, and MARS MRI. Dr. Kwon stated the importance of having an early and accurate diagnosis, since late revision surgeries can have poorer outcomes. In addition, further optimization, standardization and validation for MARS MRI needs to be done. Further longitudinal imaging studies are necessary to determine the natural history of progression of soft tissue changes within a patient.

Smith & Nephew also presented data on using MARS CT to analyze patients with their hip resurfacing device, and discussed limitations of MARS MRI and ultrasound.

During the discussion, a few of the items highlighted by the panel were: prevalence of pseudotumors in metal on polyethylene hips compared to metal on metal hips; alternative possible imaging modalities for patients with contraindication for MRI; the practicality of using MARS MRI to evaluate patients across the country today; standardization of MARS MRI protocol; and the sensitivity and specificity of MARS MRI. There was also debate about at what intervals and in what patients soft tissue imaging is indicated.

Open Public Hearing:
During the open public hearing, several surgeons and researchers, including a hospital group, presented data on MoM hip systems. In addition, several associations, patient advocacy groups, and patients made statements about MoM hip system.

Metal Ion Testing Methodology:
To introduce the scientific session on "Metal Ion Test Methodology", FDA gave an overview of some of the analytical issues that impact the precision, reproducibility and accuracy of metal ion test results and issues that impact their clinical interpretation. As a guest speaker, Robert Jones, PhD from the Center for Disease Control detailed the importance of patient sample type selection, prescreening of sample

containers, proper sample collection methods, properly determining the limits of detection and limits of quantitation of the methods, sources of analytical interference in cobalt and chromium measurements, appropriate quality control procedures, the importance of participation in a proficiency testing program, criteria to properly interpret a test result and criteria to consider for selecting an appropriate clinical laboratory to perform the testing. The speakers on behalf of Corin and Smith & Nephew presented data from several studies on metal ion levels in patients and discussed the use of metal ion test results for patient management. The panel then deliberated on the clinical utility of the test measurements. Some of the topics discussed during the deliberation were: the appropriate patient population; frequency of the testing; clinical thresholds; the need for new studies; the difficulty of the methods; and sample types.

Outcomes: Local and Systemic Complications:

Dr. Carlos Lavernia began the session on local and systemic complications. Next, Dr. Joshua Jacobs began his presentation reiterating that MoM hip systems are heterogeneous devices and need to be evaluated separately as each device has different patient populations, different surgical techniques and clinical outcomes. Dr. Jacobs highlighted that any adverse local or systemic complication in a MoM hip patient is an adverse local tissue reaction (ALTR). The ALTR may present as osteolysis, delayed hypersensitivity, soft tissue masses or necrosis or some combination of the three. He reiterated Dr. Jeremy Gilbert's message from the previous day that when wear occurs, corrosion occurs and then outlined potential methods of monitoring wear. Moving on to metal ion testing, Dr. Jacobs highlighted interlab variability and the need to conduct an analysis of consistency of lab results within the United States. On systemic effects, Dr. Jacobs gave an overview of the handful of published case reports of metal toxicity from total hip replacements highlighting that there have been just as many reports of metal toxicity from ceramic on metal total hip replacements as MoM hip replacements. Dr. Jacobs discussed that hypersensitivity exists, but we are not sure how prevalent it is and we are not sure if patch testing is indicative of a deep tissue response.

The third invited guest speaker of the session was Dr. Katherine Squibb whom outlined determinants and mechanisms of metal toxicity. During the discussion of Chromium she highlighted the differences between Cr^{+3} and Cr^{+6}. For cobalt, renal toxicity is a concern, making the ion levels very important.

Smith and Nephew and DePuy Orthopedics also presented on local and systemic complications.

Dr. Jacobs was asked by the Panel to explain his preference for serum over whole blood metal ion testing and emphasized metal ion testing is to look at comparative values. The Panel also discussed the valency of chromium. The Panel members also expressed concerns of wear corrosion at the head/neck and stem/neck junctions and if such a reaction would also be prevalent in metal on polyethylene hips.

Summary:

Within the context of potential imaging and ion tests, the panel deliberated on follow up recommendations for symptomatic and asymptomatic patients with MoM total hip systems and with MoM hip resurfacing systems.

One issue highlighted by the panel was the limitations in currently available data to answer the questions of most concern, which include questions about the interpretation of imaging and ion testing results, questions about the performance of these devices relative to therapeutic alternatives, and better explanations for the sources of heterogeneity in outcomes. The panel also stressed the need for some prospective longitudinal, randomized controlled studies to fill in some of these gaps.

The panel's general consensus was that it should be left to an individual surgeon in discussion with his/her patient to choose the best technology. The panel did not reach a consensus regarding a recommendation for a particular patient population for whom a MoM hip was felt to be the best choice of an implant.

The panel discussed in depth the importance of fully informing patients about the potential risks of MoM hip systems prior to the procedure. The panel agreed that the labeling contraindications that are already listed on the products, include those for patients with renal insuffiency, immunosuppressed patients and females of childbearing age, are appropriate. They noted the importance of conveying to the surgeon that the procedure is technically demanding and it is difficult to achieve optimal implant positioning.