March 1, 2010

Margaret A. Hamburg, MD
FDA Commissioner
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Docket Number: FDA-2009-N-0575

Dear Commissioner Hamburg:

The American Academy of Orthopaedic Surgeons (AAOS), the Pediatric Orthopaedic Society of North America (POSNA), and the Scoliosis Research Society (SRS) representing over 17,000 Board-certified surgeons, welcome the opportunity to comment on the Food and Drug Administration's (FDA) open public meeting on the issue of the incorporation of new science into regulatory decision making within the Center for Devices and Radiological Health (CDRH). It was particularly unfortunate that the meeting coincided with inclement weather in the Washington, DC area, which caused a significant decrease in participation at the meeting/conference call and likely changed the tenor of the meeting.

As advocates for our patients, AAOS/POSNA/SRS members endeavor to provide the highest quality orthopaedic care. We will provide comments on the Center's specific case studies and follow with general comments and suggestions on ways to incorporate emerging science into regulatory decision making within the CDRH.

Case Study 1:

- Scenario A: CDRH clears Device X for marketing through the 510(k) process. Device X is cleared for a specific intended use. Several years later, a pattern of Medical Device Reports (MDRs) that have been submitted to CDRH calls into question the safety of the device when used in the long term for its cleared use. A number of other devices of the same type and with the same intended use as Device X are on the market when this new safety information comes to light. There is also a device of the same type, Device Y, under review through the 510(k) process. The 510(k) submission for Device Y cites Device X as a predicate.
- Scenario B: CDRH approves Device Z for marketing through the PMA process on the basis of favorable results in a pivotal clinical trial. Several years later, a compelling peer-reviewed publication reports that an attempt to replicate these clinical trial results was unsuccessful. A number of other devices of the same type and with the same intended use as Device Z are PMA-approved and on the market when this article comes to light. There is also a device of the same type and for the same intended use, Device Q, under review through the PMA process.

Questions of Interest:

- (A)(1) When CDRH gains new scientific information about a particular product or type of product, what should the criteria be for changing CDRH's expectations of the evidence necessary for pre- or postmarket regulatory decisions, keeping in mind our mission to protect and promote the public health, as well as our statutory and regulatory framework?
- (A)(3) When such changes are warranted, how should CDRH apply them to devices currently under review?
- (A)(4) When such changes are warranted, how should CDRH apply them to products currently on the market?

AAOS/POSNA/SRS Response:

The criteria for changing CDRH's expectations of the evidence necessary for pre- and postmarket regulatory decisions will always depend on the degree of risk the device poses to patients. The CDRH must calculate a new benefit/risk ratio when learning of new scientific information. The AAOS/POSNA/SRS would encourage that the FDA contact each manufacturer and discuss the nature and mechanism of deficiency or failure when encountering a problem with medical devices.

With long term use, some devices may be prone to degradation. If stakeholders are informed of a problem, they may be able to change the design, the material, or the manufacturing process to prevent the problem from occurring in the future. As such, communication with manufacturers, engineers, and surgeons is paramount.

In cases where the CDRH has a postmarket safety signal with only one manufacturer's product in a class of devices, it would seem inappropriate to apply the same level of scrutiny to all of the manufacturers of the same product type. The CDRH might need to review the data for substantial equivalence to the predicate device. Such a review (of device Y with respect to its predicate, device X) may differentiate the safety issue to X, but not Y.

Newer products should not be held to a higher standard than marketed products. Therefore, we suggest that the Center apply the same regulatory decisions and framework to all of the products, assuming that the CDRH is receiving a safety signal on all marketed products of a particular device type and that the signal is a significant threat to public health. Additionally, the AAOS/POSNA/SRS recommend that manufacturers ensure proper training for physicians and surgeons using medical products to assure that devices are being used appropriately.

Case Study 2:

A company works with CDRH to design a three-year clinical trial to study an investigational device, Device J. The trial will assess the effect of Device J on a particular measurable variable, which is meant to be a surrogate for a specific clinical outcome. In

year two of the trial, CDRH learns from other compelling peer-reviewed studies in publication that the surrogate does not reliably track the expected clinical outcome. Consider the following variations on the case above:

- Scenario A: Prior to this point, CDRH has not cleared or approved any other devices on the basis of clinical trials using this surrogate endpoint.
- Scenario B: Prior to this point, CDRH has cleared or approved a number of other devices on the basis of clinical trials using this surrogate endpoint.
- Scenario C: At this point, there are several other investigational devices that are being tested in clinical trials using this surrogate endpoint.
- Scenario D: At this point, CDRH is reviewing a PMA for an investigational device that was tested in a clinical trial using this surrogate endpoint.

Questions of Interest:

- (A)(1) When CDRH gains new scientific information about a particular product or type of product, what should the criteria be for changing CDRH's expectations of the evidence necessary for pre- or postmarket regulatory decisions, keeping in mind our mission to protect and promote the public health, as well as our statutory and regulatory framework?
- (A)(2) When such changes are warranted, how should the Center communicate them to industry, consumers, and other external constituencies? Should CDRH have a new regulatory paradigm for communicating with outside parties?
- (A)(3) When such changes are warranted, how should CDRH apply them to devices currently under review?

AAOS/POSNA/SRS Response

The FDA is responsible for protecting and promoting public health. As devices are classified according to risk based criteria, the criteria for changing CDRH's expectations of the evidence necessary for pre- or postmarket regulatory decisions need to be formulated according to a risk-based scheme as well. A change in criteria/requirements by CDRH after an agreed upon trial is in progress should require justification, based on safety and effectiveness considerations. This would then be open to discussion and, if necessary, appeal. In scenario B, the clinical performance of similar approved devices will be relevant to CDRH decisions and should be considered. A change in requirements should hinge on safety issues unless there is clear evidence that efficacy has become an issue.

The AAOS/POSNA/SRS recommend that the Agency follow the Centers for Medicare & Medicaid Services (CMS) model for Open Door Forums[1] that allow transparent communication from the public to the Agency on policy issues pertaining to new evidence.

[1] Link: http://www.cms.hhs.gov/opendoorforums/

The AAOS/POSNA/SRS advocate for more communication to stakeholders through the various strategies currently in place. Continued development of the FDA website is encouraged particularly to aid in user-friendly approaches to the design of the content. As discussed during the public meeting, if the CDRH intends to be significantly more proactive, more resources will be needed.

The AAOS/POSNA/SRS stand ready to work with the Center and Agency; in fact, many of the societies in the Alliance of Specialty Medicine (Alliance), of which AAOS is a founding member, have ongoing interactions with the CDRH. Several medical specialty societies have established registries and are willing to provide critical postmarket information to the CDRH.

Case Study 3:

CDRH clears Device W through the 510(k) process. At the time of clearance, it is considered to be state of the art. A number of other devices of the same type and with the same intended use as Device W soon come onto the market. Over the following years, devices of the same type and for the same intended use evolve through several generations, leading to a new state of the art device with a significantly more favorable risk-benefit profile than that of Device W and similar older devices. Device W and similar older devices are still in market use. There is also a device of the same type, Device R, under review through the 510(k) process. Device R has a similar risk-benefit profile to that of Device W, and the 510(k) submission for Device R cites Device W as a predicate. Consider the following variations on the case above:

- Scenario A: The newest devices are shown to be safer than Device W and similar older devices, but seem to have roughly the same level of effectiveness.
- Scenario B: The newest devices are shown to be more effective than Device W and similar older devices for their intended use, but seem to have roughly the same level of safety.
- Scenario C: The newest devices are shown to be both safer and more effective than Device W and similar older devices.

Questions of Interest:

- (A)(1) When CDRH gains new scientific information about a particular product or type of product, what should the criteria be for changing CDRH's expectations of the evidence necessary for pre- or postmarket regulatory decisions, keeping in mind our mission to protect and promote the public health, as well as our statutory and regulatory framework?
- (A)(3) When such changes are warranted, how should CDRH apply them to devices currently under review?
- (A)(4) When such changes are warranted, how should CDRH apply them to products currently on the market? For example, how should CDRH treat "first-generation" products as new and improved versions are developed?

AAOS/POSNA/SRS Response

As stated previously, the Agency is charged to protect and promote the public's health. Medical device clearance requires demonstration of safety and effectiveness, often by substantial equivalence to a cleared or approved device. Substantial equivalence does not require that a device be better than a previously cleared predicate device, or even that it be equal to the predicate.

Medical products will continue to evolve and will likely provide better or different safety and effectiveness profiles as more scientific knowledge and as more clinical experience is acquired. The AAOS/POSNA/SRS trust that patients and health care providers together choose the appropriate treatment(s) by considering both risks and benefits.

The FDA has precedent for changing regulatory requirements on marketed products, for instance with bone graft substitutes. In 2006, the Center for Biologics Evaluation and Research (CBER) produced a guidance[2] establishing criteria for human cellular or tissue-based products to be regulated solely as human tissue. All manufacturers with marketed products were required to provide the CDRH with testing data if their product did not meet the definition of minimally manipulated allograft tissue.

Products should only be removed from the U.S. market if they pose a significant safety hazard. Life enhancing and life saving products should be differentiated in the CDRH's risk assessment and subsequent warranted actions. Additionally, the FDA should ensure that the marketing of medical products, whether it is direct-to-consumer or directly to medical professionals, is truthful and fully reflects indications, contraindications, warnings, precautions, and side effects.

Case Study 4:

A device currently under review within CDRH is a first of a kind device that uses a new bioactive material with unique properties.

Questions of Interest:

- (B)(1) Assessing the safety and effectiveness of a novel technology can be challenging because the extent of information on and the level of understanding of the technology's risk-benefit profile or manufacturing process is less mature than that of a technology for which there is extensive "real-world" experience. What steps should CDRH take to assure that novel technologies or novel uses of existing technologies are safe and effective, without creating barriers to innovation, keeping in mind our statutory and regulatory framework?

[2] Guidance for Industry and FDA Staff: Minimal Manipulation of Structural Tissue Jurisdictional Update. Sept. 20, 2006. Food and Drug Administration. Accessed at: http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/ucm073396.htm

- (C)(1) With current resources, what proactive steps should CDRH take to address gaps in staff-members' knowledge about new science and reduce uncertainty in science-based regulatory decision making?

AAOS/POSNA/SRS Response

Case Study 4 describes a novel device, likely necessitating a premarket approval application. The CDRH should assess the relevant risks and benefits through its internal research, outside consultants if needed, and other available resources. Over time, registries may help to confirm (or discredit) approval decisions. The use of registries will provide the community with more long term data about medical science. As such, the federal government should provide grants so that more specialty medicine registries can be generated and allow for collection of longitudinal safety and effectiveness data.

The use of post-market surveillance and registries is the best way to continuously monitor device safety and effectiveness. The orthopaedic community was pleased that the Agency for Healthcare Research and Quality (AHRQ) issued a funding announcement for an orthopaedic registry network. AAOS surgeons anticipate collaboration between the new orthopaedic registry network and the American Joint Replacement Registry (AJRR).

The CDRH has been extraordinarily proactive in developing or expanding postmarket programs during the past few years. The AAOS/POSNA/SRS commend the development of the MedSun (Medical Product Safety Network) program to promote early reporting and improve patient safety efforts.

The AAOS/POSNA/SRS eagerly anticipate the development of the Unique Device Identification (UDI) database and system. The globally harmonized UDI system will assist in numerous patient safety efforts and aid in the collection of information into registry databases.

General AAOS/POSNA/SRS Comments

FDA's Mandate

In 1976, the Medical Device Amendments (MDA) was signed into law and established device categorizations. Unless the device was found substantially equivalent to the pre-amendment device, the product was automatically placed in Class III, and subject to premarket approval. Therefore, MDA served two purposes: 1) to safeguard the public health and 2) to expedite the introduction of new devices.

The Food and Drug Administration's mandate is to promote and protect public health. As the CDRH categorizes medical devices according to the risk posed to the patient, the degree of risk for life saving devices must be clearly differentiated from life enhancing or sustaining devices.

During the public meeting, some speakers called for the FDA to add comparative effectiveness to their mandate. Furthermore, one speaker called for devices to be labeled inferior to others and advocated for fewer products on the market.

The AAOS/POSNA/SRS would not support any additional mandate for the FDA. The AHRQ is the lead federal agency charged with comparative effectiveness issues and recently received a large investment in funding as part of the American Recovery and Reinvestment Act (ARRA). The FDA has been involved with these AHRQ and other HHS initiatives in this area, so it would seem unwise and unnecessary for the FDA to add comparative effectiveness to its mandate.

The AAOS/POSNA/SRS would find few instances where it is appropriate to label devices as inferior to another device. As was mentioned by one of the speakers at the public meeting, subgroups of the patient population may well benefit from the continued availability of a device that, using population-wide data, might nonetheless seem inferior to a newer device.

During the public meeting, CDRH staff raised the possibility of listing on the labeling the predicate devices on which a device had received approval through the 510K process. We agree that including device genealogy in the labeling could be helpful to physicians and surgeons.

Transparency and Predictability

Predictability is important for all stakeholders and the CDRH should make every effort to define a level playing field. Some panelists at the February 9th meeting suggested arbitrarily switching 510(k) applications to pre-market approval applications. This type of action is neither transparent nor predictable and should be avoided unless there are significant safety concerns about the device. Once a pathway to clearance or approval is defined or agreed upon, there should be no arbitrary changes in FDA's requirements. The Agency should be required to show cause essentially based on safety issues, for requiring changes to either a premarket notification or premarket approval study.

The AAOS/POSNA/SRS encourage early communications to stakeholders about problems with devices. The AAOS and the Alliance of Specialty Medicine (Alliance) will provide staff contact information to the Office of Surveillance and Biometrics for various CDRH postmarket programs. Moreover, Alliance member organizations will assist the CDRH with scientific expertise when problems arise in their particular medical specialty. AAOS/POSNA/SRS and Alliance members serve on the Center's Medical Devices Advisory Committees for premarket issues and will assist the CDRH as clinical liaisons, when contacted for a specific assignment.

Registry issues

Throughout the health care reform debate, the AAOS/POSNA/SRS and the Alliance have been opposed to the creation of a National Medical Device Registry (NMDR), which

could be subject to subpoena or FOIA requests by personal injury attorneys and then used to exacerbate the ongoing medical liability crisis. No protections for any physician level data were included in the legislative language, which was ill-advised at a time when the public overwhelmingly supports comprehensive tort reform. Additionally, we caution against any duplication of post-market programs, including those authorized but not yet implemented in the Food and Drug Amendments Act of 2007.

Specialty societies are collaborating with the CDRH on a regular basis with involvement in cardiac and other registries. Several Alliance member organizations are actively working to establish specialty specific registries, and interactions with CDRH will be ongoing.

Coordination/collaboration with other agencies

The HHS annual budget devotes billions of dollars to infrastructure. The HHS agencies, including the National Institutes of Health (NIH), the AHRQ, the CMS, and FDA, must continue to work collaboratively to ensure the best science is available for use. The NIH-FDA regulatory science initiative to develop and use new tools, standards and approaches for the assessment of medical product efficacy, safety and quality, is a great example of collaboration. HHS agencies should also continue coordinating or relying on work done by other federal agencies outside of HHS, such as the National Institute of Standards and Technology (NIST).

Workforce issues at FDA

Many surgical specialties are in need of pediatric surgeons working within the FDA. The POSNA and the SRS pledge to assist the FDA in filling those positions, when they become available. We again encourage the FDA towards greater use of clinical liaisons for special projects.

Personalized Medicine

As we enter an era of personalized medicine, we recognize that devices work differently for different population subgroups and that outcomes can be affected by surgeon training and experience. The wealth of scientific knowledge continues to grow every year. The AAOS/POSNA/SRS imagine that once more knowledge is acquired; some medical products previously taken off the market could once again emerge as safe and effective for the U.S. market.

Staff Education

The AAOS/POSNA/SRS recommend that CDRH develop a Regulatory Site Visit Training Program model for “high risk” medical devices to allow personnel to visit both medical device companies and hospitals. Similar to the Center for Biologics Evaluation and Research’s program for complex biologics, this training program should be intended to give FDA regulatory review, compliance, medical, and other relevant staff an opportunity to visit medical device manufacturers. These visits are intended to allow FDA staff to directly observe routine manufacturing practices and to give Agency staff a

better understanding of the medical device industry, including its challenges and operations.

In addition, the AAOS/POSNA/SRS recommend the Regulatory Site Visit Training Program be enhanced with opportunities to visit hospitals – including academic and private practice settings – to understand the challenges of using medical devices in the operating room. Real world understanding will inform the Agency on development of better product labeling to reduce errors and tailor the Agency's decision-making to meet the needs of protecting the public health.

Education for FDA employees should be ongoing. Technology changes rapidly, and FDA employees must ensure that they understand the clinical relevance of medical devices. Many physicians from societies within the Alliance already participate in FDA staff college education and are ready and willing to continue participation.

The FDA should make funding available for medical society meetings and workshops to support continued education for FDA staff. Additionally, the FDA should continue to pursue education and training by other than full time employees by using student interns and externs and by allowing FDA staff to take sabbaticals.

We also strongly encourage the FDA to increase the resources available for Staff College sessions. The AAOS, through the Orthopaedic Device Forum, has worked with surgeons and FDA staff to provide insight to the clinical uses of products such as spinal interventions, soft tissue substitutes, and orthobiologics, including bone graft and bone graft substitutes. Based on the positive feedback from participants we believe these programs are mutually beneficial and strengthen the clinical liaison between the Agency and medical societies.

Postmarket Surveillance

The AAOS/POSNA/SRS encourage training for surgeons using new technology to ensure that they understand the appropriate use of the device. The role of widespread postmarket surveillance is increasingly important as clinical trials may not establish the long term performance of medical devices in large populations or in specific patient subgroups. Some issues in orthopaedics, such as wear-related debris generated by total joint replacements and its adverse impact on surrounding tissues, may not be reproducible in the laboratory or in animal models and may affect such a small number of patients at a relatively long follow-up time of a decade or longer that no reasonably sized and designed trial will provide a safety signal.

Medical/surgical standards development

The enhanced use of existing standards and identification/prioritization of needed standards would be beneficial for the medical community. The AAOS/POSNA/SRS request that the Office of Device Evaluation (ODE) provide a list of standards priorities for the American Society for Testing and Materials (ASTM) and the International

Standards Organization (ISO) similar to the current practice of listing annual guidance priorities in the Federal Register. The AAOS/POSNA/SRS support the continued development of medical/surgical standards and provides financial support for the American Society for Testing and Materials (ASTM) and International Standards Organization (ISO) activities. All of the Biomedical Engineering and Biological Implants committee members are members of the ASTM. Additionally, AAOS members actively engage in the development of needed orthopaedic and tissue standards.

Guidance document development

The AAOS/POSNA/SRS agree with the recommendations of the 2007 Science Board that the CDRH should develop and spend more time on guidance documents, standards, and other written publications, archiving and retrieval systems, with written precedent files so that once a decision is reached, subsequent reviewers are informed of the previous decisions. The AAOS has commented repeatedly over the last few years on the decreased publication of guidance documents following the establishment of the 2002 Medical Device User Fee Act (MDUFMA) performance goals.

The MDUFMA instituted progressively challenging performance goals for the review of pre-market approval applications, biological license applications, and 510(k) submissions. Prior to the passage of MDUFMA, the timelines for meeting performance criteria were more discretionary. In order to meet the performance goal timelines, priorities were shifted with fewer resources devoted to guidance document development. Thus, the diminished production of the CDRH guidance documents was an unintended consequence of the MDUFMA of 2002.

Delays in publishing guidance documents are of significant concern to the AAOS/POSNA/SRS. We recognize that that differing priorities exist within the FDA divisions, offices, and centers. However, the AAOS/POSNA/SRS suggest that the Agency devote considerably more resources to the development of needed guidance documents.

The AAOS/POSNA/SRS acknowledge the success of the utilization and development of FDA guidance documents in aiding transparency. These documents assist in enhancing predictability for manufacturers, FDA reviewers, and other stakeholders in the development of pre-market device and notification submissions, and expedite the review process. Manufacturers often cite receiving different interpretations for reviews of nonetheless similar products. Guidance documents assist in the standardization of FDA policy and interpretation.

Additionally, guidance documents are often used as special controls to support a down-classification. The AAOS/POSNA/SRS encourage the CDRH to move forward with down-classifications (from Class III to II) on technologies with good safety and effectiveness profiles so that the Center can more adequately use its resources. The

AAOS/POSNA/SRS stand ready to assist the FDA in revising and creating guidance documents to address critically important clinical information.

Physician-directed applications

Physician-directed applications also known as off-label use continue to be a part of physicians' arsenal in the practice of medicine. While most physicians would undoubtedly prefer to use medical devices according to the intended labeling, it is not always possible. Therefore, the off-label use of devices continues to be a significant part of the art and science of medical practice.

Both benefits and risks exist with off-label use. Benefits include the ability to provide care to patients who would go untreated without off-label use, such as many pediatric patients. Risks include a potential for increased medical liability problems and in some instances the lack of a science base for the intended use of the device. In 1998, the Supreme Court issued a judgment in *Buckman v. Henney* affirming that physicians' may use therapies if they believe they are in the best interests of their patients.

Physicians attempt to practice evidence-based medicine using the best available clinical evidence. Off-label use may be standard of care in some instances when an evolving science base is found in the medical literature. Numerous societies' members within the Alliance are witnessing patients opting out of treatment on perceived experimental use of standard of care applications, especially within pediatric populations.

AAOS/POSNA/SRS would like to work with stakeholders to attain "on-label" indications, particularly for pediatric indications. In 2007, Congress passed the Pediatric Medical Device Safety Act into law and recognized that pediatric devices needed to be developed and that surgeons were often treating patients with off-label uses because there was no other option. We propose cohort studies, literature reviews, meta-analyses, when possible and the development of objective performance criteria be used to support appropriate labeling claims. Physicians and surgeons endeavor to teach important uses for devices, but are currently prohibited due to the off-label status of the indication.

Health care costs

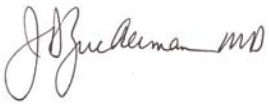
During the course of the health care debate, all parties and stakeholders agreed that the current cost trajectory is unsustainable. In consideration of the current 510 (k) issues, most analysts would agree that restrictions of the pre-market notification program will only add to the increase in health care costs of the nation. Devices going through the premarket approval process cost considerably more than those with substantial equivalence claims. There was a lack of data substantiating safety concerns presented by any stakeholders at the public meeting. As the FDA has yet to define significant safety concerns with the 510 (k) processes, we suggest that the premarket notification process has worked extraordinarily well with few exceptions. The AAOS will provide an extensive comment on the 510 (k) process within the next month.

Conclusion

The AAOS/POSNA/SRS thank you for the opportunity to comment on the incorporation of new science into regulatory decision making with the Center for Devices and Radiological Health. We recommend a minimum of thirty days for a comment period following an open public meeting. Providing less than a reasonable comment period disadvantages stakeholders from having time to reflect on the arguments presented at the meeting as well as shortening the time for circulation of draft comments within their organization or community. We realize that the CDRH established an aggressive timeline so that they may unveil a strategy in May 2010. Nonetheless, we believe that the best public policy is assembled after hearing from a multitude of stakeholders views', and we believe that CDRH is more likely to obtain comprehensive and helpful comments from a broader cross-section of stakeholders if a longer comment period were allowed.

We look forward to working with you on these important endeavors. If you have any questions, please contact Jeanie Kennedy, Manager of Government Relations at the American Academy of Orthopaedic Surgeons at 202/548-4148 or kennedy@aaos.org.

Sincerely,



Joseph D. Zuckerman, MD
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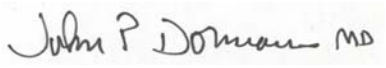

John P. Dormans, MD
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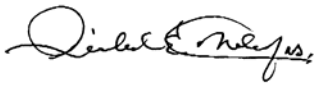

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