



AMERICAN ACADEMY OF
ORTHOPAEDIC SURGEONS

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2211 8 FEB 19 P12:44

317 Massachusetts Avenue NE
Suite 100
Washington, D.C. 20002-5701

P. 202.546.4430
F. 202.546.5051

www.aaos.org/dc

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Andrew C. von Eschenbach, M.D.
FDA Commissioner
Division of Dockets Management (HFA-305)
Food and Drug Administration (FDA)
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Dear Dr. von Eschenbach:

The American Academy of Orthopaedic Surgeons (AAOS/Academy), representing over 17,000 Board certified orthopaedic surgeons, welcomes the opportunity to comment on the FDA Science Board Science and Technology Subcommittee Report, "FDA Science and Mission at Risk" [Docket 2007N-0489]. The report provides a comprehensive internal and external assessment of the FDA's ability to use science and technology to support their current and future regulatory needs. The findings are revelatory and affect all national consumers. The Academy is grateful for the contributions of all thirty-three subcommittee members, including AAOS Fellow Cato T. Laurencin, M.D., Ph.D. The AAOS agrees with most of the findings of the subcommittee report and will anticipate the implementation of the recommendations.

At the January 29, 2008 House Energy and Commerce Oversight and Investigations subcommittee, Peter Barton Hutt, former Chief Counsel of the FDA, noted that Congress has enacted more than 100 statutes during the last 20 years that directly impact the FDA, without providing money or personnel to implement them. Also during the past 20 years, FDA appropriations have resulted in a gain of 817 employees and a loss of more than \$300 million to inflation.¹ The AAOS will address some areas in the report in addition to other specific issues not expressly addressed in the report.

SUPPORT FOR INCREASED APPROPRIATIONS

The AAOS is pleased that the Science Board report has acquired the interest of Congress and encourages that the findings be used to generate increased appropriations from the Legislative and Executive branches of the government. The Agency is chronically underfunded compared to other federal health agencies while one quarter of consumer

spending is expended on products under the purview of the FDA. Unfunded mandates cannot continue at the levels that have occurred in the past. The Agency must have needed resources to address public health needs such as critical inspections for human tissue processors. Furthermore, an over reliance on user fees from industry is not beneficial for consumer confidence in the FDA.

Scientific staff must have the resources to attend necessary professional medical society conferences. Heretofore, the FDA resources have not been adequate to ensure participation at educational venues. The AAOS has extended numerous invitations to Agency staff for orthopaedic symposia and workshops and were often informed that funds were not available for travel. Additionally, the Orthopaedic Device Forum has generated half-day educational sessions working through the FDA staff college. However, the onsite educational sessions have been infrequent due to Agency resources. The staff college sessions are modestly budgeted and of benefit to multiple Centers at the FDA. The AAOS suggests that additional resources allocated for educational sessions will benefit the science base of the FDA.

INFORMATION TECHNOLOGY INFRASTRUCTURE

Information technology (IT) improvements are some of the FDA's greatest and most immediate needs. As outlined by Dale Nordenberg, MD, also before the House Energy and Commerce Oversight and Investigations subcommittee,² information technology at the FDA has three distinct purposes. First, FDA staff must be able to communicate with each other via email, the computer network, Internet, and other administrative systems. Second, the FDA must provide the scientific and technical expertise to review certain technologies that utilize IT within their medical products such as computerized robotic surgical systems. Lastly, the FDA must assess data to determine the safety and efficacy of drugs, devices, or biologics. The pre-market and post-market data should be linked to allow for an early determination of safety signals.

Data must be available electronically rather than in paper form. The Science Board report states that the Center for Veterinary Medicine spends \$1 million per year for the storage of paper alone.³ Data should be integrated for information on pathogens, chemical toxicity, and adverse event reporting. Furthermore, the FDA needs more resources to work with groups such as Kaiser Permanente to bolster its post-market surveillance efforts.

The Academy recommends that the FDA dramatically increase their IT budget to reflect the administrative and regulatory functions covering the broad range of medical products, foods, and consumer goods that the Agency oversees.

OFFICE OF SCIENCE AND ENGINEERING LABORATORIES (OSEL)

Research conducted in OSEL should support the needs of the FDA Centers to aid in the regulatory and review processes. Rather than basic science research conducted at the National Institutes of Health, OSEL should conduct applied research on specific product or engineering issues. OSEL could assist in post-market surveillance issues by assessing

the cause(s) of problem devices such as occurred during the St. Gobain zirconia femoral head and Sulzer Inter-op acetabular shell hip implant recalls.

CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)

Data in the CDER has largely been warehoused and generally inaccessible in an electronic format. As the FDA has a critical need to assess the total product lifecycle, the FDA must be able to integrate pre- and post-market data. Furthermore, the FDA should integrate active surveillance systems rather than relying on passive surveillance for safety signals.

The AAOS disagrees with the statement that the Advisory Committee process offers little value in providing useful insight and oversight.⁴ The Drug Safety and Risk Management Advisory Committee has repeatedly made beneficial suggestions to FDA staff and provided examples from the physicians' expertise. Many of the scientific staff have not practiced medicine or have relinquished their practices. The Academy agrees that it is increasingly more difficult for the FDA to qualify physician experts as special government employees and will address this further under the conflicts-of-interest section.

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH (CBER)

Particularly in CBER, expertise is needed in nanotechnology and genomics as the science base continues to progress. The AAOS wholeheartedly supports the Science Board recommendation to continue the multidisciplinary teamwork with the Center for Devices and Radiological Health on issues such as combination products or tissue engineering. Laboratory collaboration with National Institutes of Health personnel is proving to be beneficial and should continue even after the CBER move to the White Oak facility. Finally, the Academy believes support for a human tissue safety testing branch to focus on microbial safety should be one of the Agency's highest priorities.

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH (CDRH)

The AAOS agrees with the recommendations of the 2001 Committee on Science and CDRH:⁵

- CDRH should establish an electronic base for liaison functions and internal and external expertise inventory.
- CDRH should develop...more time spent on guidance documents, standards and other written publications, and archiving and retrieval systems, with written precedent files so that when a decision is reached it does not only remain in the "mind" of the reviewer.
- ... CDRH needs to streamline processes that encourage scientific growth within the staff and the maintenance of scientific expertise; these processes need to provide for a more inviting career path and a reward structure for scientific personnel, and will require a reallocation of budget resources so that stated goals of staff growth can occur.

- CDRH should develop a plan in collaboration with other Centers for the evaluation of combination products.

Further, The Academy will highlight some Critical Path Initiatives which are critical for the functioning of the Center:

- While CDRH understands that many new important technologies are now emerging, it is not adequately equipped to understand the science of these technologies.
- In particular, CDRH must expand its use of outside individuals for performance of scientific reviews, visiting scientists in residence, and outside reviews of CDRH's science projects as part of its science prioritization process.
- There remains a need for increased cross-Agency and inter-Agency alliances with intramural research programs and extramural research that can aid CDRH in its research mission.
- Staff development continues to be an issue of concern at CDRH. Attendance at scientific meetings to understand new technology and to present scientific research to colleagues appears to be hindered.

The AAOS looks forward to working collaboratively with staff at CDRH to further their development of these critical needs.

GUIDANCE DOCUMENT DEVELOPMENT

The AAOS has commented repeatedly over the last few years on the lack of published guidance documents following the creation of the 2002 Medical Device User Fee Act (MDUFMA) performance goals. The MDUFMA demanded 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 Center for Devices and Radiological Health (CDRH) guidance documents was an unintended consequence of the MDUFMA of 2002.

With respect to the orthopaedic community, the AAOS submitted a draft document on the *Clinical Trial Design for Hip Replacement Systems* on January 29, 2004. Additionally, the AAOS entered the *Proposed Guidance Document for Pre-clinical and Clinical Trial Design for Cervical and Lumbar Disc Replacement Systems* into a FDA docket on March 10, 2005. While we are encouraged to hear that the Division of General, Restorative, and Neurological Devices anticipates movement on these draft guidances in fiscal year (FY) 2008, delays in publishing guidance documents is of significant concern to the AAOS. While FDA officials concede that there are differing priorities within the divisions,

offices, and centers, the Agency must generate more resources or define another pathway for the development of needed guidance documents.

The AAOS is encouraged that the structure of the 2007 device user fees and review goals in the Food and Drug Administration Amendments Act of 2007 (FDAAA) provide for more stable operating procedures. The Academy acknowledges the success of the utilization and development of FDA guidance documents. These documents assist in predictability and transparency for manufacturers in the development of pre-market device and notification submissions, as well as expediting the review process. Manufacturers often cite receiving different interpretations of product reviews. Guidance documents assist in the standardization of FDA policy and interpretation. Additionally, guidance documents are often used as special control documents to support a downclassification. The AAOS stands ready to assist the FDA in revising and creating guidance documents to address critically important, clinical information.

SPECIFIC GUIDANCE DOCUMENTS

Conflict-of-interest draft guidance

While it is unusual for the AAOS to make this request and have commented previously, we ask that the FDA immediately withdraw the Draft Guidance on Procedures for Determining Conflict of Interest and Eligibility for Participation in FDA Advisory Committees [Docket 2007D-0101]. The conflict-of-interest language in FDAAA mandates a reduction of special government employees with conflicts-of-interests for FDA advisory committees over the next five years. While the FDA was attempting to be responsive to Congress as hearings for the renewal of MDUFMA were occurring in March 2007, the language in Title VII of FDAAA was agreed to by both chambers of Congress and signed into law by the President on September 27, 2007. Therefore, if the FDA implements the published draft guidance, the regulatory framework laid out in the guidance document will be more stringent than required by either Congress or the Administration. The AAOS strongly objects to this as a matter of policy.

The Academy is aware that the Circulatory System Devices and the Orthopaedic and Rehabilitative Devices advisory committees are the most difficult to empanel as conflicts-of-interest are common. The AAOS finds sufficient inconsistency in defining a limit of \$50,000 for disqualification from panel participation. The type and size of each manufacturer can be quite variable. As the 2007 conflict-of-interest draft is currently written, there would be no difference in distinguishing holdings of a multinational company with a broad range of products from that of a single product company. The product approval of a new medical device for a large, diversified company will ultimately have a negligible effect on the share's value, whereas a FDA approval for a company's only product may have huge implications on the value of that particular stock.

In any case, as conflicts-of-interest are of vital interest to the American public, we ask the Commissioner to require the Executive Secretaries of FDA advisory committees to document the amount of time spent on procuring special government employees for advisory panels, the nature of the potential conflicts, the number of candidate special

government employees considered for each meeting, and any other relevant data. It will be particularly important to provide accurate data to Congress during the next reauthorization of drug and device user fees.

The FDA must have the latitude to appoint experts to the panel where the need for the individual's services outweighs the potential for a conflict-of-interest created by the financial interest involved. The FDA contracts with special government employees to seek perspectives and expertise beyond its in-house staff and to convene balanced, informative, and impartial advisory committee meetings.

At present, medical societies find restrictions on FDA panel nominees increasingly difficult due to a number of criteria that must be met in addition to considerations for conflicts-of-interest. FDA panels must have geographic, ethnic, and gender diversity. For clinical representation, panel members should be practicing physicians for many years, have knowledge of the conduct of clinical trials, statistics, intricate knowledge of specific anatomy (if on a device panel), they may need to assess the biomechanical forces imposed on the anatomy if a device is implanted, cellular biology to determine wear on the devices, and knowledge of American Society for Testing and Materials (ASTM) and International Standards Organization standards. Members may also need to be knowledgeable about packaging and the effects of gamma radiation on medical device components.

Further, if a device is being reviewed, the panel member may need to be familiar with a certain type of surgical approach, for example, an anterior approach for a cervical spinal disc. Knowledge of blood loss and blood replenishment is also crucial during discussion of medical devices. Indeed, with some new technologies including gene therapies, only a few world-wide experts may be familiar with that particular technology and they will generally all be conflicted.

Certain panel members or potential panel members may be conflicted with interests representing an entire medical specialty. For instance, the AAOS is aware of several orthopaedic laboratories which conduct research on biomaterial standard specifications, cellular biological applications, and orthopaedic joint mechanics. Each researcher receives funding from virtually every orthopaedic manufacturer in the U.S. to support the operational and research needs of their laboratories. The material conflicts may run into the hundreds, and the orthopaedic community considers personnel such as this to have such broad-based material conflicts so as not to be conflicted. In the orthopaedic community, researchers with multiple conflicts are important resources for the FDA Orthopaedic and Rehabilitative Devices Panel. One researcher served as a former panel chair person and another served on the panel for over a decade. Extremely qualified participants of this nature will be prevented from serving on future FDA panels if the 2007 draft guidance is adopted thereby preventing a wealth of expertise and experience to be utilized by the federal government.

The existing process the FDA follows for determining conflicts-of-interest is appropriate. The process is deliberative, rigorous, and has been strengthened over time. The dollar

thresholds for determining various types of conflict should be adjusted to keep pace with inflation (the FDA's recently published update to the waiver process guidance addresses the issue of the financial threshold). Additionally, the extent of a special government employee's exposure should be commensurate with their overall earnings. One advisor's conflict may be minimal compared to his/her overall income, or one's conflict may be indirect because the financial gain accrues to his/her sponsoring academic institution, and not the scientist.

Off-label use draft guidance

Following the sunset of provisions in the Food and Drug Administration Modernization Act (FDAMA) on September 30, 2006, dissemination of journal articles with off-label use of medical products has largely been halted under threat of the prosecution of marketing practices. While a few abuses occurred under the prior statute, off-label use remains commonplace during the practice of medicine. For various regulatory and financial reasons, manufacturers determine that they will not seek additional label claims or generate new products.

The Academy encourages further development on the FDA's draft guidance "Good Reprint Practices and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drug and Approved or Cleared Medical Devices." The draft guidance may allow reprints from peer-reviewed research from reputable medical journals that were not significantly influenced by manufacturers or those with financial conflicts. Peer-reviewed medical literature is the current gold standard to inform physicians of the best evidence treatment decisions.

FDA guidance would provide the Agency's current thinking on the dissemination of truthful, non-misleading scientific information. Off-label use is rampant in the practice of medicine and in some cases considered the standard of care. Certain populations such as pregnant women and children have not been granted entry into clinical trials, therefore much of their medical care is delivered by the off-label use of medical products. Additionally, cancer patients are often prescribed many off-label therapies.

The use of antibiotic bone cement in primary hip arthroplasty is one example of off-label use in orthopaedics. In the U.S., several companies manufacture antibiotic bone cement but this combination product (regulated as a device) is indicated for use in revision hip surgery. As reported in the Swedish registry, in 92,675 patients undergoing primary, cemented total hip arthroplasty, the use of antibiotic bone cement was a significant factor in the reduction of deep infection.⁶ Excellent data from the Swedish and Norwegian hip and knee registries and disseminated in journal articles are used by orthopaedic surgeons to support the most optimal treatment decisions for patients, in the U.S.

The accelerated dissemination of this information is in the best interests of patients, physicians, health care delivery systems, and our nation as a whole. The AAOS looks forward to providing comments on this draft guidance as soon as it is made publicly available.

STANDARDS DEVELOPMENT

As codified in the FDAMA in 1997, FDA officials were directed to meet with representatives of foreign countries to reduce the burdens of global regulation and harmonize regulatory requirements. Additionally, officials were directed to engage in efforts to accept mutual recognition agreements relevant to the regulation of devices and good manufacturing practices between the European Union and the United States. FDAMA recognized national and international standards in the review of medical devices. The AAOS thanks the FDA for its leadership on global harmonization task forces and the advances in standardization accomplished over the past few years. The Academy encourages continued participation in standards and global harmonization activities.

DEVELOPING TECHNOLOGIES

The AAOS has a particular interest in nanotechnology and its applications for tissue engineering. Nanotechnology poses interesting challenges for the health care community and regulators. The potential for novel treatments are apparent, but risks must be mitigated. Understanding the long-term biological consequences of nanotechnology products will be critical to public's acceptance. *In vivo* and *in vitro* tests will need to be developed to predict human reaction to some nanotechnology products.

Some animal studies purport that exposure to nanoparticles is inflammatory to lungs, and that some particles relocate to the blood, brain, liver, heart and spleen.⁷ Authors from the National Institute for Occupational Safety and Health argue that because little is known about the toxic health hazards of nanoparticles *in vivo* and *in vitro*, pharmacokinetic and toxicological studies are mandatory before large-scale industrial production occurs.⁸ Federal agencies, including but not limited to the National Institutes of Health and the Department of Defense, will need to allocate considerable federal funding for research on nanotechnology applications.

The Science Board subcommittee found that the FDA cannot adequately monitor the development of new medical products nor evaluate the safety of existing products because the Agency cannot keep up with scientific advances in nanotechnology, genomics, wireless healthcare devices, medical imaging, robotics, cell and tissue-based products, regenerative medicine, and combination products. The Academy respectfully requests that the FDA address these inadequacies immediately. Medical products are being developed that will be able to substantially help patients and the FDA must be ready to meet the regulatory and scientific challenges.

UNIQUE DEVICE IDENTIFICATION (UDI)

The AAOS was integral member of the Advancing Patient Safety coalition that worked with members of the legislative branch to include UDI language in the FDAAA. The Agency must promulgate regulations to identify medical devices as required by the new statute. The Academy encourages the timely development of such regulations and looks forward to commenting on the proposed rule in fiscal year (FY) 2008.

DIRECT-TO-CONSUMER (DTC) ADVERTISING

While the Division of Drug Marketing, Advertising, and Communications resides within the Center for Drug Evaluation and Research, the AAOS is concerned that not even one full time equivalent is assigned to medical device marketing. As the marketing and advertising of devices continues to increase, staff is needed to assess the appropriateness of the advertising of medical devices.

There are substantial differences between pharmaceuticals and medical devices, including: a significant price differential, the selection of a device requires a much higher level of judgment and skill than the choice of a branded vs. generic drug; and most importantly, the potential negative consequences to the patient and the surgeon are substantial if an inappropriate device is chosen for a particular patient or procedure. Unlike drugs, the choice of an implant cannot be easily substituted if the result of the surgery is undesirable.

DTC advertising of devices may not inform patients about the differences in product design, composition of materials, strength of the devices, or proper clinical indication. Potential patients may not have access to post-market surveillance data or understand issues relating to device performance and safety. Surgeons choose devices to meet an individual patient's needs. For example, implant wear is a significant issue for orthopaedic surgeons. Patients may not be aware of the appropriateness of certain devices for their particular health conditions or health status.

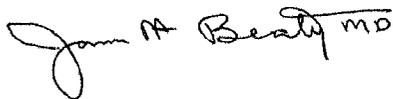
Despite the potential benefits of DTC advertising to empower patients with information regarding their health and encouraging patients to seek treatment, results from a recent orthopaedic study⁹ suggest significant issues. The findings relate that 77 percent of surgeons felt that patients exposed to DTC advertising are confused or misinformed about the appropriate treatment for their orthopaedic condition; have unrealistic expectations regarding the benefits of a particular surgical technique or implant; are not aware of the additional costs, potential risks, and complications associated with a particular implant or surgical technique; and are less likely to pursue surgery as a result of viewing the advertisement. Furthermore, study results indicate that patient exposure to DTC advertising has the potential to create friction between doctors and patients and may increase the length of office visits which is costly to the healthcare system. Seventy-four percent of respondents believe that DTC advertising had an overall negative impact on their relationship with patients.

CONCLUSION

The AAOS appreciates the opportunity to comment on this critically important document from the Science Board and commends you on commissioning this assessment of the structure and functioning of the FDA. During the subcommittee investigations, the FDA Science Board Science and Technology subcommittee found that greater external oversight was needed in charting the future of FDA than presently exists. Advisory committees are quite useful for input on specific products or guidance documents however, the Advisory Committee program as it is currently structured, does not lend

itself to provide continual input to the Agency. External input across the FDA Centers is needed to foster and ensure change at the Agency. The AAOS stands ready to assist the FDA on a continual basis. We look forward to working with the Agency on efforts to provide for a more stable science and regulatory base that will enable better patient care.

Sincerely,



James H. Beaty, MD
AAOS President

¹ House Energy and Commerce Oversight and Investigations subcommittee. Statement by Peter Barton Hutt: http://energycommerce.house.gov/cmte_mtg/110-oi-hrg.012908.Hutt-Testimony.pdf

² House Energy and Commerce Oversight and Investigations subcommittee. Statement by Dale Nordenberg, MD: http://energycommerce.house.gov/cmte_mtg/110-oi-hrg.012908.Nordenberg-Testimony.PDF

³ FDA Science and Mission at Risk, Report of the Subcommittee on Science and Technology. November 2007, Appendix D6 http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4329b_02_02_FDA%20Report%20Appendices%20A-K.pdf

⁴ FDA Science and Mission at Risk, Report of the Subcommittee on Science and Technology. November 2007, Appendix E10 http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4329b_02_02_FDA%20Report%20Appendices%20A-K.pdf

⁵ DA Science and Mission at Risk, Report of the Subcommittee on Science and Technology. November 2007, Appendix H7 http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4329b_02_02_FDA%20Report%20Appendices%20A-K.pdf

⁶ Malcau H, Herberts P, Ahnfelt L: Prognosis of total hip replacement in Sweden. Follow-up of 92,675 operations performed 1978-1990. Acta Orthop Scand 64:497-506, 1990.

⁷ Nemmar, A, Hoylaerts, MF, Hoet, PH, Vermynen, J, Nevery, B, Size effect of intratracheally instilled particles on pulmonary inflammation and vascular thrombosis. Toxicol Appl Pharmacol. 2003 Jan 1;186(1):38-45.

⁸ Gwinn, MR, Vallyathan, V, Nanoparticles: Health Effects- Pros and Cons, Environ Health Perspectives, Dec 2006, Volume 114, Number 12, 1818-25.

⁹ Bozic, KJ, Smith, AR, Hariri, S, Adeoye, S, Gourville, J, Maloney, WJ, Parsley, B, Rubash, HE: The 2007 ABJS Marshall Urist Award: The Impact of Direct-to-Consumer Advertising in Orthopaedics. Clinical Orthopaedics and Related Research, May 2007;458:202-19.