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Chief Executive Officer

John C. Lewin, M.D.

July 14, 2011

The Honorable Margaret A. Hamburg, MD
Commissioner
Food and Drug Administration
5630 Fishers Lane, room 1061
Rockville, MD 20852

Re: Circulatory System Devices Panel of the Medical Devices Advisory Committee Meeting Announcement; Pre-Market Approval Application for Edwards SAPIEN™ Transcatheter Heart Valve

Dear Dr. Hamburg:

The American College of Cardiology (ACC) is pleased to submit comments in response to the pre-market approval application of Edwards Lifesciences with respect to the SAPIEN Transcatheter Heart Valve. The College is a 40,000-member nonprofit medical society composed of physicians, nurses, nurse practitioners, physician assistants, pharmacists and practice managers, and bestows credentials upon cardiovascular specialists who meet its stringent qualifications. The ACC is a leader in the formulation of health policy, standards and guidelines, and is a staunch supporter of cardiovascular research. The College provides professional education and operates national registries for the measurement and improvement of quality care. We appreciate the opportunity to furnish input to the Food and Drug Administration (FDA) and the Circulatory System Devices Panel of the Medical Devices Advisory Committee on this important new technology.

The conventional strategy for severe aortic stenosis is surgical aortic valve replacement. Over the past decade, with changes in the patient population, particularly a shift towards older patients with more co-morbidities, it has been recognized that there are many patients who choose not to undergo this procedure because of the risks and there are others who are not even offered the procedure because of markedly increased surgical risks. Medical therapy usually offered in combination with aortic valvuloplasty has not proven to be effective. Patients at particular risk are those who are frail, elderly with multiple co-morbidities and have typically been precluded from being studied in randomized trials or from surgery. Recent clinical trials in Europe and the US have now demonstrated the potential for the new treatment option of transcatheter aortic valve replacement (TAVR) for these patients who are nonsurgical candidates. The Edwards SAPIEN Transcatheter Heart Valve is one of several devices in development, and the results of the only randomized trial have now been published dealing with this specific valve technology. The ACC and its members are enthusiastic about the prospects for their patients who suffer from a predicated mortality rate of approximately 50 percent if they are deemed to be non-surgical candidates. The clinical trial documents a decrease in mortality for those patients when they are treated with TAVR, providing

The mission of the American College of Cardiology is to advocate for quality cardiovascular care — through education, research promotion, development and application of standards and guidelines — and to influence health care policy.

an opportunity for cardiovascular specialists to offer hope to patients and families where there has been little in the past.

It is of fundamental importance to the ACC that cardiovascular specialists provide the highest quality patient care. One component of that high quality care is ensuring responsible disbursement of this new technology. As described below, TAVR is a complex and multifaceted procedure. It requires a high level of expertise and experience. To ensure rational and responsible dissemination of this new technology, government, industry and medicine will need to work in harmony. We look forward to this opportunity to work together to make high quality patient care available to the appropriate patient population in the appropriate setting from appropriately experienced operators conducting the necessary follow-up.

Opportunities to collaborate

The practice of cardiovascular medicine has changed dramatically over the last 10 years. The advent of diagnostic imaging and other technological advances have brought with them significant reductions in morbidity and mortality. Government, industry, and medicine have all played important roles in fostering the technologies and the climate that have allowed for these tremendous improvements in patient care. However, as these new technologies have emerged, government, industry and medicine have struggled with how best to disseminate and provide access to these new procedures. The ACC believes that all three groups are important to this process and must come together to ensure appropriate availability and use. Responsible dissemination of a new technology requires input and collaboration among industry and the applicable specialty societies. The manufacturer is generally best equipped to educate physicians on the details of the specific device, while the applicable specialty society or societies are best equipped to educate physicians regarding the particular disease state and the various therapies available for treatment of that disease, as well as to provide the framework for pre-procedural planning, procedural performance, and follow up. Government must help to facilitate these interactions in the appropriate context and encourage collaboration among all affected parties. In these modern times, novel implantable devices like aortic valves require that the roles, relationships and supportive interactions between federal agencies and professional societies be revisited with a creative and pragmatic eye.

Frequently, the physician community is criticized for its inability to coordinate and collaborate in order to present a unified response to requests regarding a wide variety of issues. In this instance, the organizations representing the various physician specialties involved in transcatheter aortic valve therapies have worked diligently to develop a collaborative set of clinical documents to guide those professionals furnishing the services. We recognize that transcatheter valve therapy is a hybrid of multiple very advanced medical disciplines, and as such, collaboration between those disciplines is critical. Most recently, the ACC and the Society for Thoracic Surgery (STS) released a high-level “Professional Society Overview” addressing transcatheter valve therapy that was published in both the *Journal of the American College of Cardiology*¹ and the *Annals of Thoracic Surgery*.² This document sets the stage for a series of documents that will address the

¹ Holmes DR, Jr., Mack MJ. Transcatheter valve therapy: a professional society overview from the American College of Cardiology Foundation and the Society of Thoracic Surgeons. *J Am Coll Cardiol* 2011;58:445–55.

² Holmes DR Jr., Mack MJ. Transcatheter valve therapy: a professional society overview from the American College of Cardiology Foundation and The Society of Thoracic Surgeons. *Ann Thorac Surg* 2011;92:380-9.

issues critical to successful integration of this new procedure into medical practice in the United States.

Moving forward, the Society for Cardiovascular Angiography and Interventions (SCAI) is leading development of a multi-societal competency statement on institutional and operator requirements. The ACC Foundation (ACCF), the Society for Thoracic Surgery (STS) and the Association of American Thoracic Surgeons (AATS) have joined the effort. Additionally, the ACCF is leading a second multi-societal writing effort focusing on pre- and post-procedural patient management issues pertaining to TAVR, including patient selection. Along with AATS, SCAI and STS, seven other societies are being invited to participate in the document in order to provide a comprehensive, balanced view of the various aspects pertaining to this new technology. As representatives of cardiologists, surgeons, interventional cardiologists, and other members of the multidisciplinary heart team as noted below, these organizations are highly respected and trusted by the professionals who perform the services. Thus, documents drafted and reviewed by their peers will have great influence over behavior.

The ACC strongly believes that the medical community has an important role to play in the dissemination of new technology. It is incumbent upon the physician community to act responsibly by setting forth guidelines as mentioned above, developing multidisciplinary teams with representation from all affected specialties, selecting appropriate patients, providing guidance regarding facility requirements, coordinating amongst itself to ensure providers have the necessary education and conducting effective follow-up and study.

Multidisciplinary heart teams

Recent studies have paid increasing levels of attention to multidisciplinary professional heart teams. Treatment of valvular heart disease is an ideal opportunity for cardiovascular specialists to collaborate. The complexities of structural heart disease require cardiovascular specialists with varying areas of expertise to coordinate and rely on one another. The concept is already in use in heart transplant centers. There, patient treatment decisions and care are managed by experts in heart failure transplants, ventricular assist devices, immunosuppression, echocardiography and anesthesia. The TAVR heart team consists of primary cardiologists, interventional cardiologists, cardiac surgeons, noninvasive and heart failure cardiologists, echocardiographers and cardiac imaging specialists, cardiac anesthesiologists, nurse practitioners, physician assistants, research coordinators, administrators, dietary and rehabilitation specialists and social workers. Each component of the care team will need to develop and implement specific protocols, depending on the individual patient and specific technical procedure.

Candidates for transcatheter valve therapy typically have long been identified as individuals suffering from cardiovascular disease and thus have been treated by primary cardiologists. These individuals will continue to care for the patient before and after the procedure, working in concert with the subspecialists, communicating with patients and families and advocating for the patient's needs and desires. Imaging specialists are particularly critical owing to the lengthy list of potentially involved modalities: two- and three-dimensional transthoracic and transesophageal echocardiography, vascular computed tomography with three-dimensional reconstruction, cardiac magnetic resonance imaging, diffusion-weighted magnetic resonance imaging of the brain and transcranial Doppler imaging. While not all may be required for each procedure, all must be available in the event of known complications. Additionally, heart failure specialists are essential components of the team because of the increased likelihood that potential candidates for the procedure also have a component of left ventricular dysfunction, which can complicate the assessment of the severity of aortic stenosis. Heart failure specialists will also need to assist with

the assessment for the potential reversibility of the left ventricular dysfunction following the procedure. As described above, it becomes clear that no one subspecialty of cardiology can perform this procedure in isolation; instead, it must be performed using a multidisciplinary, team-based methodology.

Patient selection

Careful patient selection is essential to achieving positive outcomes for any cardiovascular therapy. It is especially critical for novel therapies, such as TAVR. Physicians on the multidisciplinary heart team must work in concert with each other to determine whether individuals are appropriate candidates for this new procedure. Given the complexities of the procedure, patient selection is not a simple task. Many questions remain unanswered regarding specific patient selection criteria. Thus, it is important that FDA approval for the device be limited to those patients who fit the criteria where positive outcomes were demonstrated in the trial. That said, it is equally important that the outcomes in other patient populations continue to be studied for the potential implications of the new procedure for the patient care guidelines. As discussed earlier, the ACCF, in collaboration with the other aforementioned societies, continues to develop documents addressing issues pertaining to patient selection.

Facility requirements

Today, many cardiac surgical centers and catheterization laboratories have a low volume of structural heart disease cases. Based on an ACC review of Medicare claims data, fewer than 37,000 aortic valve replacements were performed on Medicare patients in all of 2010. When compared with the 185,030 coronary artery bypass grafts that were performed during that same time period, it is clear that few centers have significant volume of this service. Yet, studies indicate that outcomes for patients undergoing surgery for valvular heart disease have a direct relationship to center procedure volume. Given the complexity of these cases, it is even more important that facilities performing TAVR have significant experience and adequate resources. Thus, the ACC supports development of centers with specialized expertise in TAVR. The level of complexity and resources required to perform TAVR mean that not all facilities that wish to furnish the procedure should do so at this time. Similar to transplant centers, patients will benefit most from experienced centers that perform a comparatively substantial number of TAVR procedures. The centers should initially have characteristics that match the criteria of those participating in the clinical trials.

The centers will also need to have either a modified conventional cardiac laboratory or a hybrid operating suite. Because of the nature of the procedure, the room used needs to be able to accommodate both equipment used for catheter-based procedures and surgery, along with all associated imaging equipment. Additionally, the sterility required for surgery must be achievable.

Where these new hybrid rooms should be located within the facility has yet to be determined. Proximity determines the breadth of equipment available to the physicians, as well as the depth of expertise. Placement in an operating suite means wider access to surgical equipment and personnel, whereas placement near the catheterization laboratories allows for increased availability of catheterization laboratory equipment and personnel. Both cardiologists and surgeons will need to have access to the hybrid room, making it critical for all affected to be involved in the process of determining its location.

Additionally, post-procedure patient care will need to be centralized in one location with access to personnel experienced with hemodynamic assessment and large-bore catheter and sheath vessel access issues, surgical incisions and chest drainage tubes. Given the host of potential issues and complications, surgical units may be best situated to care for these patients.

Operator training and education

The ACC and STS support the division of training into two components: education regarding the disease and range of therapies and training on particular devices. Industry has specific regulatory requirements to train users on particular proprietary devices, and manufacturers are the ones with the best information regarding their particular devices. However, we firmly believe that it is the responsibility of the affected specialty societies to conduct the disease state and treatment options education. To that end, the ACC, STS and others are working together to develop such programs. Currently, the only US-based operators with experience in TAVR work at the 30 to 40 clinical trial sites, thereby limiting the ability of physicians to be trained to perform the procedure. We will need to draw heavily on the experiences gained through the PARTNER trial and experiences of our counterparts in Europe regarding training requirements and setting standards for operator competence. There is much still to learn, and thus, it is important that determinations regarding these requirements and guidelines be left to the professional societies for definition after a thorough review of all available evidence.

Post-procedure follow-up

Critical to learning about outcomes and patient safety is a mechanism for collecting data on patients who receive the procedure and have the devices implanted in them. Clinical trials can provide information on immediate outcomes and even short-term or intermediate follow-up in a limited patient population using a particular device in a procedure performed by a specific pool of physicians at specific facilities. While these trials provide invaluable information, they are expensive to conduct and do not necessarily provide the full gamut of information needed.

Registries can help to provide the long-term follow-up that can be used to develop safety signals, as well as gather additional evidence regarding patient outcomes, operator training requirements and facility set-up. ACC's National Cardiovascular Data Registry® (NCDR) is one example of such a registry. In 1997 the ACC launched the NCDR as a result of its exploration of various strategies for collecting and implementing clinical data to improve cardiovascular care. The outgrowth of that effort focused on quality patient care through standardized measurement of clinical practice and patient outcomes. Then, as now, NCDR is committed to including clinicians and care providers in its leadership and to using standardized, clinically relevant data elements and scientifically appropriate methods to collect, analyze and report clinical outcomes.

Today, more than 2,200 hospitals nationwide participate in the NCDR. As the US' preeminent cardiovascular data repository, the NCDR provides evidence-based quality improvement solutions for cardiologists and other medical professionals who are committed to measurement, improvement and excellence in cardiovascular care. As a trusted, patient-centered resource, the NCDR has developed clinical modules, programs and information solutions that support the areas of cardiovascular care where quality can be measured, benchmarked and improved to make a difference in patients' lives.

NCDR data has been studied for a variety of purposes, including consistency with guidelines,³ appropriateness,⁴ and comparative effectiveness, to name a few.⁵ The FDA has long been a supporter of NCDR, providing funding for the Improving Pediatric and Adult Congenital Treatment (IMPACT) Registry and development of a possible atrial fibrillation registry. NCDR is also a participant in the FDA's Sentinel Initiative, looking at methods of drawing on registry data as a mechanism of providing safety signals to the FDA. We look forward to continuing to work collaboratively on these initiatives.

ACC is currently working to compare the effectiveness of revascularization strategies by linking NCDR and STS' clinical database with administrative databases, including the Social Security Death Master File and the Centers for Medicare and Medicaid Services (CMS) Provider and Analysis Review data. While currently no valvular disease registry exists, both ACC and STS are committed to working jointly to develop the tools needed. Linking the clinical databases with the aforementioned administrative databases will, in effect, create a national registry of valvular heart disease similar to those that exist in Europe. This will not be an inexpensive initiative; however, we believe it to be an essential component of quality patient care, outcomes analysis and comparative effectiveness research. As such, we call on relevant parties to commit to working together to create and fund this initiative. Because of a variety of concerns, we stop short of requesting that the FDA require Edwards to fund a registry operated by a third party, but we strongly urge the FDA to use its authorities to assist the ACC and STS in convening discussions with the appropriate parties regarding the development of such a system.

There are certain efficiencies to be gained from using registries, such as NCDR, for post-market research and surveillance. It increases the collaboration between industry and the professional societies, providing an increased level of credibility to the data and findings. NCDR has the ability to conduct site recruitment, patient randomization and data audits. Additionally, because of the existing registry structure, there are a large number of pre-defined data elements and procedures already available to those interested in using NCDR for a transcatheter valve therapy registry. That said, additional data fields can be added as necessary.

NCDR powers what has the potential to be a powerful research resource: the National Cardiovascular Research Infrastructure (NCRI). Created through a federal grant, the ACC Foundation, in partnership with the Duke Clinical Research Institute, is working to build a cardiovascular research infrastructure, including the standards for data definitions and elements. Among its goals, the NCRI project aims to develop a large simple clinical trials platform to solicit and advance research questions that fill critical evidence gaps, as well as an integrated electronic repository of tools and programs to assist clinical research site activities accessible by a web-based informatics structure. Ideally, NCRI powered by NCDR has the potential to streamline data collection, so industry, government and research entities are not competing for valuable limited resources.

³ Chan PS, Patel MR, Klein LW, et al. Appropriateness of Percutaneous Coronary Intervention. JAMA 2011; 306(1):53-61.

⁴ Al-Khatib SM, Hellcamp A, Curtis J, et al. Non-evidence-based ICD implantations in the United States. JAMA 2011; 305(1):43-49.

⁵ Funded by a National Heart, Lung, and Blood Institute American Recovery and Reinvestment Act Grant, the ASCERT Study represents a unique collaboration between the ACCF and STS to study the comparative effectiveness of percutaneous coronary intervention and coronary artery bypass graft surgery in patients with stable coronary artery disease.

Conclusion

The ACC recognizes the excitement in the cardiovascular community of the potential availability of new technology to patients with limited treatment options and applauds the efforts of those seeking to bring this new procedure to the US. We understand the need to ensure only the highest quality patient care is provided, especially to the frail patient population at issue today. The ACC is pleased to see that the excitement over the new technology is tempered by these efforts to ensure responsible dissemination of it. We are working hard to align our efforts with our fellow specialty societies – STS, SCAI and AATS – as a way of doing our part to ensure that the physician community is prepared to provide high quality care using the newest technology and techniques to patients with cardiovascular disease. The ACC appreciates the efforts of the FDA to date and looks forward to continuing to work with the Agency to protect the interests of cardiovascular patients.

The ACC appreciates the opportunity to provide the FDA's Advisory Panel on Circulatory System Devices with input pertaining to the pre-market application for approval of the Edwards Lifesciences SAPIEN Transcatheter Heart Valve and would welcome the opportunity to discuss this input further. We look forward to working with the FDA on this and future issues. Please direct any questions or concerns to Lisa P. Goldstein at (202) 375-6527 or lgoldstein@acc.org.

Sincerely,



David R. Holmes, Jr., M.D., F.A.C.C.
President

Cc: Jack Lewin, M.D. – CEO, ACC