

The Honorable Joseph R. Pitts

- 1. In your testimony, you note that the U.S. innovation ecosystem is eroding, can you elaborate as to what is contributing to this weakening? What actions should Congress take to reverse this trend? Based on your experience as an executive in the medical device industry, what do you think are the ingredients to ensure we have a robust innovation ecosystem?***

The U.S. innovation ecosystem is eroding: As this Committee has heard in prior “21st Century Cures” testimony, there are a variety of factors contributing to the weakening of the innovation ecosystem. Recent data from the National Venture Capital Association help to illustrate the decline. Between 2007 and 2013, medical device investments fell by a total of 40 percent. In 2007, there were 98 companies amassed approximately \$576 million in initial venture capital. Since then, there has been a 50 percent reduction in the number of device companies receiving initial venture capital investment and an approximately 70 percent drop in the amount of capital invested. In 2013, the U.S. witnessed the lowest level of medical device initial funding activity in more than two decades. Last year, only 44 new venture device companies raised a total of \$163 million compared to of which there was 98 companies in 2007.

Strict regulatory requirements and lengthy review processes have contributed to this erosion: From Edwards Lifesciences’ viewpoint, the regulatory approval process and the U.S. reimbursement system have been significant barriers to timely market access for new, innovative technologies. The increasingly burdensome scientific inquiries from FDA require more robust and longer clinical trials, which are costly and delay opportunities for firms to recoup their investment. This hampers the ability to have innovative technologies available in the US in a timely fashion. For example, we’ve invested more than 10 years in the pursuit of U.S. approval for the SAPIEN transcatheter heart valve platform, dedicating time, resources and significant funding to product development, clinical trials and data collection and analyses. Due to the large amount of clinical data required for approval in the US, the SAPIEN valve was obsolete in Europe and was replaced by the next version of the device (SAPIEN XT) in Europe two years before the original SAPIEN valve was approved in the US. The ability of the patients in the US to obtain life sustaining medical devices lags significantly from other countries due to the large clinical studies that are required for approval in the US.

Inspections of manufacturing sites should be a more collaborative effort between FDA and manufacturers. FDA should be encouraged to take a more risk-based approach to compliance inspections. In other countries, governments partner with the local companies to help them comply with regulations.

Additionally, heightened scrutiny of the economic value of new technologies at the earliest stages of their development create a significant risk that a technology may not meet third-party payers’ (e.g., Medicare) requirements for coverage and adequate payment. It is imperative to recognize that medical device innovations become more effective and more efficient with time, experience and device improvement. If we hold new innovations to the same unforgiving standard that we hold well-established technologies that have been honed to near perfection over decades, we will miss opportunities to help American patients with new and transformational technologies. We need a system that takes into account the healthcare system’s learning curve, and does not shut the door to evaluation on day one, while always maintaining patient safety along the way.

Costly and time-consuming data gathering requirements, combined with uncertainty regarding reimbursement amounts and coverage, yield uncertainty and delays in a company's ability to begin sales of its product and recoup its investment. These barriers and risks created by the U.S. regulatory and reimbursement system discourage investment in new, breakthrough technologies.

Necessary ingredients to a robust innovation ecosystem: Based on the Edwards experience, there are essential elements to fostering an ecosystem that incentivizes curiosity and rewards innovators who develop new therapies for patients, including: patient/physician needs clearly communicated and ascertainable, ready access to capital and supportive economic climate, functional, timely and predictable regulatory processes, a reimbursement system that welcomes novel therapies as they undergo a continuous improvement process, and strong intellectual property protection.

Actions Congress should take to reverse the erosion of our innovation ecosystem: Congress can provide FDA greater support and – where necessary – changes to statute to provide the agency authority to streamline the product approval process. Some areas where FDA has begun to make improvements is through proposals to streamline the clinical trial IDE approval process, reduce legal complexity between the different hospital IRBs, incorporate patient preferences and tolerance for risk into the decision-making process, and allow for the use of surrogate endpoints or data from sources outside the U.S. during the safety and efficacy evaluation. In addition, FDA has proposed to shift some of the pre-market review process to the post-market setting. And efforts have been made to improve reviewer training, better align the pre and post-market surveillance functions at FDA, and allow for expedited appeals of FDA decisions. We support these initiatives, and they need to move faster. Congress can help in that regard, particularly in the form of providing additional financial resources for FDA to expedite these new initiatives.

Additionally, CMS's authority could be expanded to allow for the encouragement of medical technology innovation. Our healthcare system must be willing to pay for promising new technologies, even though they may appear costly in the near term. If there is a significant potential that a new technology can improve clinical outcomes, quality of life, and overall healthcare economics, then CMS should develop policies to allow for coverage and payment of qualifying technologies. It would stimulate innovation if CMS provided coverage and adequate payment for a fixed period of time to allow a technology to develop before measuring the technology's cost-effectiveness.

2. We've heard that the amount of data that has to be collected to gain U.S. regulatory approval and reimbursement is substantial. Can you give us an idea on how much clinical and economic evidence Edwards had to generate to obtain regulatory approval and reimbursement in the U.S.?

Leading up to the initial FDA approval of the Edwards SAPIEN transcatheter aortic heart valve, our company generated a substantial amount of clinical evidence including a large, complex randomized controlled clinical trial in the US. Extensive study of this valve – including an unprecedented four *New England Journal of Medicine* papers – has demonstrated the “triple win”: a substantial and sustainable clinical benefit, extraordinary quality-of-life improvement, and cost effectiveness in inoperable patients. In fact, the SAPIEN valves are the most studied heart valve in history, with more than 300 peer-reviewed, published articles on clinical outcomes associated with the valves. There are also more than 120 cost-effectiveness and quality of life

articles related to transcatheter aortic valve replacement (TAVR). Subsequent indications and different access routes (used when a direct percutaneous approach is not possible) for SAPIEN were studied in registries, and we conducted a second large trial in the US – PARTNER II – for SAPIEN XT, a much improved and lower profile device that was approved by FDA in June. Accompanying these large randomized trials have been cost effectiveness and quality of life studies supporting the value of the SAPIEN family.

Following FDA approval and the Medicare National Coverage Decision (NCD) that provided reimbursement for TAVR through Coverage with Evidence Development (CED), Edwards and other TAVR manufacturers are required to support the TVT patient registry. Created by The Society of Thoracic Surgeons (STS) and the American College of Cardiology (ACC), the TVT Registry is designed to monitor and benchmark patient safety and real-world outcomes related to the TAVR procedure. The burden and cost of complying with registry requirements is not insignificant. For example, the patient data registry form for the STS/ACC TVT Registry for TAVR procedures is eight pages long and consists of more than 300 separate fields, requiring special staffing, and dedicated personnel, and hours of work to complete this exhaustive form. Many physicians have told us that it takes longer to fill out the TVT Registry form than it does to perform the procedure. In addition to the significant financial commitment manufacturers must make to support the development and ongoing operations of registries, hospitals are charged ongoing fees to participate.

3. *Based on your experience with an innovative medical technology, what improvements to the premarket approval process can be made from an evidence generation perspective?*

There are improvements that should be made to the premarket approval process and FDA is already taking on a number of initiatives to improve the regulatory processes to help improve patient access to innovative therapies. Thanks to the Food and Drug Administration Safety and Innovation Act (FDASIA), FDA has agreed to improved review and approval performance metrics tied to dramatic increases in manufacturers' user fees, and we are just beginning to see positive performance.

FDA has recently proposed a number of improvements to the premarket clinical trial process that hold promise, including:

- Streamlining the investigational device exemption (IDE) approval process
- Reducing the legal complexity and inconsistency between each hospital Institutional Review Board (IRB) through the creation of a centralized or standardized review process
- Incorporating patients' voices and tolerance for risk into the regulatory decision making process
- Addressing potentially duplicative clinical evidence through the consideration of surrogate endpoints and greater use of data developed outside of the U.S.
- Providing a more risk-based application of FDA requirements during inspections prior to an approval

Congress could encourage FDA by providing additional support to help expedite these changes and give them room to innovate.

4. As the sole manufacturer involved in the support and development of the TVT registry, what are the benefits of a registry?

Edwards Lifesciences was the first medical device manufacturer to have a transcatheter aortic valve replacement device approved by FDA. Since the approval of Edwards' first TAVR device, another company has gained FDA approval of a TAVR device. Both device companies are part of a Stakeholder Advisory Committee that meets to get updates and provide advice to the TVT Executive Committee.

There are many benefits to a registry, including real-world data collection that helps further refine appropriate patient populations. Registries can also potentially be used to remove pre-market data collection hurdles with enhanced post-market data collection. In the case of registry used with CED, it enables reimbursement in cases where payers have questions regarding the "generalizability" of the clinical data to their populations.

Other potential benefits of registry include the ability to accelerate future indication expansion utilizing registry data and the opportunity for more streamlined surveillance, if done appropriately and not in addition to existing (and generally ineffective) systems.

5. There has been a lot of positive, supportive discussion regarding patient registries. Are there any risks or costs to them? What are they?

In addition to the many benefits of patient registries, there are some risks and costs. Specifically, there is a danger that registries could become the de facto data collection mechanism for all technologies when in certain cases, level of evidence or risk is well-established and additional data collection is not needed. In some cases, the quality of data collected by the registry may be incomplete or poor, leading to inaccurate conclusions.

The centralized control of registry data could prevent independent or different research approaches from participating in the clinical and academic dialogue about the medical device. Registries may pose a barrier to access for patients who don't wish to consent to their data being collected or who refuse to participate in follow-up.

Irresponsible use of data could threaten patient access. For instance, there could be inappropriate comparison of device-to-device performance. Cherry-picking data may lead to "sensational" findings and headlines.

Registries have financial and administrative burdens. The financial burden on the healthcare system for the creation and maintenance of registries can be high, and they can be a factor in driving up the cost of healthcare. They often pose significant burdens on providers in terms of time and the cost of data management. There is also the potential for duplicative information collection.

Finally, it is important to recognize that registries cannot be left open in perpetuity – once evidence is mature, requirements need to stop so that resources can be directed to help generate evidence for new therapies.

6. *What guiding principles should be applied when deciding when and how to develop a registry?*

Registries can help improve patient outcomes by providing greater understanding of the effects of products in the real-world and can facilitate patient access to new therapies by efficiently collecting accurate data to support expanded device use and indications. Additionally, registries can provide regulators with alternative methods to monitor the performance of technologies, allowing them to shift the burden of pre-market data collection to the post-market setting. But to realize these benefits, it is important that medical device registries be carefully designed, implemented and maintained.

A key component of the recently released AdvaMed registry principles is a series of “threshold questions” intended to assure that creation of a registry is the appropriate mechanism for meeting the defined objective:

- Are there reliable data collection instruments available to collect the data needed to achieve the objectives?
- Will the registry have a stable and diverse source of funding to promote long-term sustainability?
- Is using a registry the least-burdensome means to collect the necessary data to achieve the scientific objectives?
- Do the objectives warrant the level of investment required to develop and maintain a registry?

In addition, the principles outline several key elements that should guide the development of any medical device registry, including: establishment of a data governance committee to oversee issues on ownership, access and use of any data collected; prospective registry design, to establish clear objectives and data analysis plans; policies for sharing the data collected with qualified scientific or medical researchers; and policies for the use and publication of registry data.

Registries need to be flexible on how and what is collected. As new information and methods are developed the older systems need to be replaced striving for lower costs through better efficacies. Once adequate information is obtained on an outcome, that information should no longer be collected.

Registries should also not be redundant tools for postmarket safety monitoring. If a registry can successfully perform device surveillance functions for FDA, then the devices being monitored by the registry should be excluded from other surveillance mechanisms.

The medical technology industry is committed to the principles of evidence-based medicine. Registries can be an important tool for gathering useful information about the safety and effectiveness of interventions involving medical devices and diagnostics, but only if they are designed and executed properly.

7. Does the reimbursement system hold new, game-changing innovations to unrealistic evidentiary standards?

The reimbursement system's heightened scrutiny of the economic value of new technologies at the earliest stages of their development create a significant risk that a technology may not meet third-party payers' (e.g., Medicare) requirements for coverage and adequate payment. It is imperative to recognize that medical device innovations become more effective and more efficient with time, experience and device improvement. If we hold new innovations to the same unforgiving standard that we hold well-established technologies that have been honed to near perfection over decades, we will miss opportunities to help American patients with new and transformational technologies. We need a system that takes into account the healthcare system's learning curve, and does not shut the door to evaluation on day one, while always maintaining patient safety along the way.

8. Has the FDA taken specific steps that have enhanced evidence development mechanisms and how can they be improved? If so, what are they?

April 2014, FDA released draft guidance entitled "*Balancing Premarket and Postmarket Data Collection for Devices Subject to Premarket Approval; Draft Guidance for Industry and Food and Drug Administration Staff.*" In this guidance, FDA has made efforts to clarify and update its policies concerning the balance between premarket and postmarket data requirements.

While not specifically addressed in the draft guidance document, there typically is little flexibility in requirements of IDE study design, data requirements, and follow-up for postmarket studies. Risk profile, targeted patient population, OUS clinical data, and non-clinical testing results should be taken into consideration in determining premarket IDE study design, and any postmarket studies should be designed accordingly. For example:

- Where the performance of a particular device type is well-studied, documented, and understood, the clinical data collection should be able to rely on OPCs, Patient Reported Outcomes (PROs), or other data instead of requiring a randomized controlled clinical trial.
- Similarly, if a product has excellent long-term OUS clinical performance data, this should be taken into consideration when determining clinical data collection. This is a mechanism that could be used to strike an evidence-based balance between premarket and postmarket studies. In short, IDE study designs should focus on unanswered questions rather than requiring collection of data answering questions that are well understood.

9. Have other countries created reimbursement incentives for innovation? If so, what are they and could you see them working here in the U.S.?

Yes, other countries have created reimbursement incentives for innovation. For example, when Germany – which prides itself on its innovative climate – introduced its DRG system, policymakers there recognized the potential for hospitals to focus on costs to the exclusion of potential longer-term benefits of innovation. In response, Germany created an "innovation clause," which allows for hospitals to apply for additional funds each year to pay for innovative therapies. In addition, Japan provides medical technologies a 5% bonus reimbursement payment if the product is introduced in Japan before the U.S.

The U.S. healthcare system is unique, and other countries' incentive mechanisms may not be effectively adopted in the United States exactly as designed. As the current world leader in medical innovation, the U.S. should be cautious in following the example of competitive countries. Instead, the U.S. should identify creative approaches to better valuing and driving faster innovation that will provide Americans not only transformational healthcare technologies, but also drive business growth and job creation.

The Honorable Renee Ellmers:

- 1. Mr. Mussallem, in your testimony, you mention “reducing the legal complexity and inconsistency between each Institutional Review Board (IRB) through the creation of a centralized or standardized review process”. In my district, I represent one of the largest clinical trial service providers, Quintiles. It is my understanding that without the use of a centralized IRB, clinical trials can be hindered because of the current excessive review process, where clinical trials are referred to many IRB’s. What can be done to promote or help expedite the IRB review process?***

Under current law, hospital Investigational Review Board (IRB) approval is necessary for conducting a clinical trial. In the case when a company has a large clinical trial with several trial sites, that company will have to seek IRB approval from each trial site. This can be a lengthy, complex and costly process. Additionally, if a significant change is approved by FDA during the trial, additional IRB approvals have to be obtained.

FDA and others have proposed creating an optional centralized or standardized review process, which could make the IRB approval process more efficient and reduce unnecessary cost and burden for innovation. However, this still requires centralized IRB approval, which can be time consuming. Additionally, it may not solve the problem, as hospitals frequently will not accept a centralized IRB approval, believing they are legally required under statute, regulation and policies outlined by the National Research Act of 1974. There may be alternative approaches to improving this process, and we would be happy to work with the Committee to identify and develop alternatives.

- 2. Mr. Mussallem, as a committee, we’ve heard that the amount of data that has been collected to gain U.S. regulatory approval and reimbursement is substantial. Can you give us an idea on how much clinical and economic evidence Edwards had to generate to obtain regulatory approval and reimbursement in the U.S.?***

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