

TESTIMONY

OF

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ON

**'REAUTHORIZATION OF MDUFA: WHAT IT MEANS FOR JOBS, INNOVATION AND
PATIENTS'**

BEFORE THE COMMITTEE ON ENERGY AND COMMERCE

SUBCOMMITTEE ON HEALTH

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SUMMARY OF THE TESTIMONY

- Many innovative and groundbreaking medical devices entered into the healthcare market in the past 20 years offering new diagnostic and therapeutic options to patients and clinicians
- However, there is also evidence of substantial limitations in the current pathway for regulatory approval. The low threshold of approval led to adoption of inferior devices that failed with disastrous consequences for the health and well being of Americans
- The metal on metal implants (e.g. DePuy ASR device) are bright examples of problem with 510(k) regulatory pathway that allows approval of devices based on 'substantial equivalency' when they are not. The failure of ASR device and emerging evidence of failure of other metal on metal devices has serious consequences for the public health. Tens of thousands of additional patients are expected to undergo complicated and costly major surgeries with high chance of complications and disability. In addition, these failures will cost billions of dollars to American taxpayers over the next 10 years
- The Institute of Medicine recommended elimination of 510(k) pathway. While complete elimination might not be possible it must undergo complete transformation with changes such as; (1) considered only in clinical settings where there is a room for substantial improvement in health outcomes, (2) ideally not applied to implants unless it is applied in limited group of innovative devices to correct their well known limitations, (3) there should be thorough pre-clinical testing in all circumstances
- The ASR and metal on metal examples in general show that availability of some registry data alone as a post-market infrastructure is not a substitute for faulty pre-market approval. The failures sometimes take long time to develop and large number of faulty products (e.g. implants) enter into the market with consequences for public health and well being of Americans. The ASR evidence also illustrates often more serious limitations of European regulatory process that often approves devices without any clinical evidence. In some instances there are good quality European registries jointly funded by the governments, manufacturers and physicians that can help reveal safety concerns early. However, they have limitation of their own and can only function in country specific health delivery environment
- A robust post-market infrastructure can certainly help prevent disasters or remove failing devices out of the market expeditiously. The post-market infrastructure is currently weak and needs very substantial funding. Device registries seem to be the best ways to build the post-market infrastructure. However, the registries that we have in the US today might not be suitable for building post-market infrastructure unless they provide FDA access to data, have detailed device information and based on mandatory reporting of device use and outcomes. In most instances it is more efficient to empower and provide funds to FDA to initiate registries or consortia of registries through Public Private Partnership (PPP) including participation of manufacturers, payers and hospitals. One example of this potential is the International Consortium of orthopedic Registries (ICOR) initiated by FDA. The PPPs led by FDA might be the best way to match or advance the success story of some well known European or Australian registries that are hailed as models for post-market evaluations
- We need only gradual change in pre vs post market balance and it needs to be linked to the process of building a robust post-market infrastructure/advancement of registry science. This process will ensure evidence based innovation. Only after we build a strong post-market infrastructure, accumulate evidence on device performance in real world settings we can provide recommendations on how to adjust the threshold for pre-market approval

Chairman Pitts, Ranking Member Pallone, and members of the subcommittee. I would like to thank you for the opportunity to speak today on 'reauthorization of MDUFA: what it means for jobs, innovation and patients'. Its an honor to provide this testimony today.

I am Art Sedrakyan, Associate Professor at Weill Cornell Medical College and Director of Patient-centered Comparative Research Program that focuses on safety and effectiveness of medical devices and procedures used in orthopedics and cardiovascular care; two most serious and costly public health settings in the country. I devoted my career to advancing device and surgery safety and effectiveness assessment and in the past 14 years had a chance to get exposed to worldwide academic, regulatory and manufacturing perspectives.

The FDA plays a key role in protecting the health and safety of Americans and the mission of the FDA Center for Devices and Radiological Health (CDRH) is to ensure the safety and effectiveness of medical devices.

In the past decade medical device market have been steadily increasing and became substantial portion of nation's healthcare expenditures. The devices become smaller and smarter and many innovative and groundbreaking medical devices entered into the healthcare market offering new diagnostic and therapeutic options to patients and clinicians. However, we also witnessed number of recent high profile failures of approved devices with disastrous consequences for the health and well being of Americans. While FDA leadership and tireless employees do their best to protect Americans, the mere presence of outdated regulatory pathways (low threshold) and legal loopholes associated with it create an environment that make them vulnerable to errors (overworked and understaffed), particularly when external pressures are exerted. The absence of funding for robust post-market device evaluation infrastructure is another and possibly even more important gap that is at least partially related to these failures.

Briefly about device approval: Based on the complexity and intended use the FDA determines the type and the depth of the premarket data necessary for approval. Hence devices are classified into three regulatory classes. Class I devices such as bandages, gloves or surgical instruments present minimal potential for harm to the patient and no data is required. Class II devices such as infusion pumps or ultrasound machines require special controls/standards and sometimes require clinical testing. Finally, devices with the highest level of risk are categorized as class III and include implants such as metal on metal hip prostheses, hip resurfacing systems or coronary stents). The effectiveness and safety of class III devices have to be based on a valid scientific evidence defined as *'evidence from well controlled investigations, partially controlled studies, studies and objective trials without matched controls, well documented case histories, by qualified experts, and reports of significant human experience from a marketed device'*. As you can see this is rather wide definition which allows the use of both well known pathways for regulatory approval: the Pre-market approval(PMA) and so called 'substantial equivalency' path commonly known as 510(k) pathway. While the PMA mechanism requires valid scientific evidence based clinical studies that establish the safety and effectiveness, the 510(k) path only requires that sponsor demonstrate that the device is 'substantially equivalent' to a device on the market which is called a 'predicate' device. The definition of 'equivalency' is based on intended use and technological characteristics hence open to many interpretations. Moreover, once one the market the new device can serve as a 'predicate' for another device and create vicious iterative cycle that can lead to a situation that the new device is very different than the earlier 'predicate' devices and approved without any clinical evidence or testing.

Let me support my statements based on the well known example of metal on metal hip replacement devices with a particular emphasis on DePuy ASR device. There are over 270,000 hip replacements performed in the country. While hip replacement is a very successful operation and addresses a great public health burden, some patients require revision surgery within 10 years to replace the implant due

to dislocation, wear, instability, loosening, or other mechanical failures. The bearing/articulating surface is designed to endure the contact stress and naturally is one of the key design factors to reduce the chance of revision. Hip implants with metal femoral heads with polyethylene cups were used as articulating surfaces with low revision occurrence. For example, the risk of revision in Sweden is about 5% at 10 years. On the other hand, metal on metal devices were re-introduced into the market to further reduce implant wear and subsequently the time to revision surgery. They also allow use of larger femoral heads (>32 mm vs. < 32 mm) that supposedly reduces the risk of dislocation. These devices were quickly adopted by surgeons and often used even in the elderly; one out of three elderly patients undergoing hip surgery received metal-on-metal hip implant.

These devices are approved using 510(k) path for a joint replacement despite being implantable devices. An outstanding example is the DePuy ASR metal on metal device that has been approved in August 2005 based on a 'predicate' large size Depuy 'Pinnacle' metal on metal device. When reviewing these two designs the only similarity seems to be the metal on metal bearing. The devices are otherwise not similar as evidenced by monoblock vs modular design, metal liner and neck combinations or positioning of the metal head in the socket/shell that might lead to much higher wear of the implant (Figure 1). Interestingly the ASR device was designed with the aim to allow more mobility and reduced wear.

In late 2010 United Kingdom regulatory agency (MHRA) alerted the public about severe cases of metallosis (accumulation of metal ions in the tissues) related to metal ion release from the implants. The information came from the National Joint Registry (NJR) of England and Wales. The Australian National Registry of joint implants also reported unacceptably higher implant revision occurrence related to ASR and subsequently all metal on metal implants larger than 32mm size. Furthermore, DePuy recalled over 93,000 ASR implants in August 2010. The implant recall and suffering of patients received widespread coverage in the NY Times and the scientific evidence related to metal on metal as well as other hip bearings has been summarized in our British Medical Journal (BMJ) publication. Based on the estimates

of ASR failure as well as failure rate related to other metal on metal implants we estimate that more than 50,000 American patients will undergo additional revision surgeries in the next decade. Half of the patients are elderly and covered by Medicare. The costs for taxpayers are likely to exceed billions of dollars. Aside from costs there are serious consequences for the health and well being of American patients that are yet to be fully investigated. The Figures 2-6 show that revision surgery and local adverse events suffered by patients are not trivial. These figures show only local tissue, muscle, bone death and fluid accumulation. Systemic effects of elevated metal ion levels related to metal on metal implants are in a process of being investigated.

ASR and metal on metal examples also show that availability of registry data alone is not a substitute for good pre-market approval process. While being very informative they are powerless when the failures take long time to develop. Large number of faulty products (e.g. implants) enter into the market before safety evidence becomes available with consequences for public health and well being of people. In the case of the ASR, it took about 4-5 years before evidence was accumulated, reported and product taken out of the market. This example also exposes the gaps in European system where the threshold for approval is much lower than that used by FDA. In Europe entities called notified bodies are used to perform compliance assessment. The devices are often approved without any clinical evidence. In addition, the notified bodies are fully funded by manufacturers. The system essentially relies on availability of national registry data to reveal safety concerns in post-market settings. Certainly in some instances there are good quality European registries jointly funded by the governments, manufacturers and physicians that can help reveal safety concerns early. However, these registries are not always available, have limitation of their own and can only function in a country specific health delivery environment that is not easily applicable to US setting. We certainly need much **more robust and larger registries or multinational registry consortia** to have sufficient power for safety evaluation in real world/practice settings and determine safety concerns in a timely fashion.

The Center for Devices and Radiologic Health (CDRH) at FDA has both mandatory and voluntary reporting to monitor post-market device adverse events and product problems. While manufacturers are required to directly report deaths, injuries, and malfunctions to the FDA, the device users are required to report these events to the manufacturers and only deaths to FDA. The voluntary reporting systems such as the MedWatch program, MAUDE database and Medical Product Safety (MedSun) enhanced surveillance network provide national medical device surveillance in the USA. However, these reporting systems have important weaknesses, such as incomplete, inaccurate, or unvalidated data, reporting biases related to event severity, concerns about adverse publicity or litigation, and general underreporting of events. Most importantly, denominator data are missing, which makes evaluation of safety event incidence or prevalence impossible. **Registries** are certainly the best way forward to fill the evidence gap and address the limitations of existing systems in immediate future. **Large registries or consortia of registries** capturing a variety of devices are particularly important for comparative outcomes evaluation and active surveillance. Often only large, longitudinal or even multinational registries we can provide denominator data for adverse events related to specific implants and allow proper conduct of safety and effectiveness studies particularly for rare endpoints. One evolving successful example is the FDA funded important initiative called 'International Consortium of Orthopedic Registries' (ICOR) that aims to build the foundations for a worldwide research consortium of orthopedic registries. The consortium represents 15+ nations that have existing registries with a mission to improve the safety and effectiveness of orthopedic devices and procedures through collaboration. Currently, these international registries combine to more than 3,500,000 orthopedic surgeries capturing all implantable devices on the market.

Finally, the registries that we have in the US today might not be suitable for building post-market infrastructure. Some well known professional society registries are broad, contain clinically important

data but are seriously limited in several respects. First, participation is voluntary so that findings are applicable only to those institutions desiring to improve their care quality. Second, due to the voluntary nature of participation, data validation through audit is very limited, if at all attempted. Many new technologies are adopted by enthusiasts who do not necessarily share all of the data (particularly when at the learning stage) with their societies. Third, while professional societies have strong interests in improving the delivery and quality of care, they can sometimes be conflicted when comparing device and treatment strategies that may negatively impact their profession or stakeholder. Fourth, they lack long-term follow up. Unless these registries provide FDA access to data, have detailed device information, long-term follow up and implement mandatory reporting of device use and outcomes these registries will not be the robust infrastructure that FDA needs. **In most instances it is more efficient to empower and provide funds to FDA** to initiate registries or consortia of registries through Public Private Partnership (PPP) including participation of manufacturers, payers and hospitals. The PPPs led by FDA might be the best way to match or advance the success story of some well known European or Australian registries that are hailed as models for post-market evaluations.

In the absence of robust post-market infrastructure we also need to be careful and make only gradual changes to pre vs post market balance for device approval. The changes need to be linked to the process of building large, comprehensive device registries and registry consortia and advancement of registry science. This process will ensure evidence based innovation. Only after we build a strong post-market infrastructure, accumulate evidence on device performance in real world settings we can provide recommendations on how to adjust the threshold for pre-market approval and ensure that disasters similar to metal on metal will not happen.