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Statement of Rita F. Redberg, MD, MSc.
Subcommittee on Health
House Committee on Energy and Commerce
July 17, 2011

Dear Congressman Waxman,

Thank you for the opportunity to review the California Healthcare Institute Report on medical device approvals. I am Rita Redberg, MD, MSc, Professor of Medicine and full time Faculty Member in the Division of Cardiology at the University of California, San Francisco Medical Center. I am Director of our Women's Cardiovascular Service. I am also the chief editor of the *Archives of Internal Medicine*, one of the most preeminent peer-reviewed journals of scientific research in general internal medicine, and have served on the Editorial Board of several other journals. Much of my own research has concerned the appropriate and optimal use of medical technology in patient care, and the journal frequently publishes articles related to use of medical devices. BCG provides professional consulting services to the AMA.
California Healthcare Institute subscribes to the AMA journals via a site license, in addition to the grant. The *Archives of Internal Medicine*, is published by the AMA, but my review of this report represents my individual professional opinion and does not reflect the official position or policy of my institution, or any journal or association with which I am affiliated.

FDA performance should NOT be measured in days to approval, devices are more complex now and require (more) time for a review. This report assumes the faster the FDA approves a device, the better. That may be true from the perspective of a medical device company, but it is not true from the perspective of patients. Patients need to have the assurance that the device they are going to receive has been shown to be of benefit, and that it does not have significant risks. Such studies take time, but are critical so that we can assure patients that their device, often implanted, is a better treatment than not getting the device. Just because a device is new does not mean it is innovative or "cutting-edge", such characteristics must be proven in clinical studies.

It is simply not true that randomized controlled trials (RCT) are not necessary for medical devices, as stated in Sec 2:3. It is absolutely necessary to have a RCT to determine safety and effectiveness for many devices, particularly high-risk devices, which are frequently implanted and not easily removed if it turns out that they have no benefit. RCT can be done for devices, and the most helpful and informative ones have a sham control arm to account for the powerful placebo effect of having a procedure (even an ineffective one). The importance of sham controls was seen in the recent RCT of vertebroplasty[1]. This technology was approved by the FDA and was commonly used to treat osteoporotic vertebral fractures before a randomized controlled trial with sham control was done. However, the RCT showed no benefits to vertebroplasty over sham control, meaning patients were undergoing significant risks of this surgery without any benefit. Clearly, RCT can and should be done, prior to FDA approval, to avoid such

unfortunate situations, which lead to Americans receiving devices with no known benefits and suffering significant device-related adverse events, including death.

It is difficult to evaluate the comparisons (Figure 13) of drug approval times between the European Union (E.U.) and the U.S. as basic data is not provided. The methods do not state what specific drugs were examined, how many drugs were examined, the reasons for delay in the E.U. and U.S., and any statistical analyses performed. Furthermore, there may often be valid reasons for delayed drug approval in the U.S. For example, ticagrelor is a medication which was studied in an international double-blind randomized controlled trial for patients with acute coronary syndrome. Overall results showed that ticagrelor was superior to the current standard of care, clopidogrel, which is a similar medication. However, for the subgroup of patients from the United States, ticagrelor did not show any benefit and, in fact, outcomes were better with clopidogrel.[2] The European Union has approved this medication but the FDA has not yet done so because it is reviewing further information. While on the surface this example would appear to make it seem that the FDA is slower than the E.U. in drug approval, the details show that the FDA is indeed performing its job by diligently investigating if ticagrelor is safe and effective for patients in the U.S. Without examining details for the reasons for delays in drug approval, it is impossible to judge any such differences.

The CHI/BCG report's findings differ from the study published this month in the peer-reviewed journal *Health Affairs* that performed direct drug-drug comparisons for new cancer drugs between the FDA and the European Medicines Agency (EMA).[3] This report found that all drugs approved by both agencies since 2003 were available first to U.S. patients. It found that the mean delay was 138 days and the median delay was 238 days in favor of the FDA. This publication contains information for all of the cancer drugs and their review time by both agencies; it provides data, which can be independently verified, unlike the CHA/BCG report.

Rapid approvals are often done without meaningful clinical data. For example, in 1996, the FDA approved midodrine to treat orthostatic hypotension. This drug was approved based on a surrogate endpoint – one that neither impacted patient morbidity or mortality – with the understanding that the sponsor would conduct adequate post-marketing trials to demonstrate the benefit of this medication. Fifteen years later, despite earning over a quarter billion dollars in sales, the drug's initial sponsor had not conducted the requisite clinical trials. The FDA gave several warnings to the drug company, but to no avail. However, when the FDA attempted to withdraw this medication because there were no clinical trials completed, it faced significant resistance. Therefore, midodrine remains on the market despite no assurances of safety or effectiveness only because the FDA granted accelerated approval fifteen years ago with the promise of clinical trials which never happened.[4]

Similar to drugs, important data re device approvals is not included (figures 14 and 15), such as specific device names, their complexity, the reasons for differences in time to approval, and statistical analyses to check for differences, which again make the validity of the conclusions hard to evaluate. Regardless, rapid approval for high-risk devices is not the highest priority goal. As they are often permanently implanted, it is essential that high-risk devices have adequate assurances of safety and effectiveness prior to approval. A recent report identified five medical devices approved in Europe but not in the FDA which were later found to have safety concerns or a lack of effectiveness.[5] The European Society of Cardiology recently released a consensus document which suggests several reforms for the medical device approval process in Europe because the regulatory framework there was established over 20 years ago and has not kept up with technological advances.[6] The E.U.'s device approval and recall system has been found to lack transparency as there is little publicly available data.[7]

One recent example, which demonstrates the pitfalls of fast approval for high-risk devices without the benefit of clinical data, is the Sprint Fidelis implantable cardioverter-defibrillator. This device was cleared by the FDA via the 510(k) pathway in 2004 without any premarket clinical testing. It was subsequently implanted in 268,000 patients over three years before being voluntarily withdrawn by the manufacturer for lead fractures.[8] Unfortunately, these lead fractures have already led to patient deaths

and having to make difficult choices between repeat risky procedures for lead removal or living with a fractured lead.

Due to the methodological limitations and faulty assumptions described above, it is my opinion that this study would not be accepted in a peer-reviewed medical journal.

There are certainly opportunities to improve efficiency at the FDA and make the agency more transparent. As the CHI/BCG report acknowledges, the scope of the FDA's purview has grown significantly but "federal appropriations have failed to keep up with new mandates." Increased funding and political backing for the agency will help it to perform its tasks better and help ensure that U.S. patients are getting safe and effective drugs and devices.

Sincerely,

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