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Aaron S. Kesselheim, M.D., J.D., M.P.H.
Assistant Professor of Medicine

BRIGHAM AND WOMEN'S HOSPITAL

Division of Pharmacoepidemiology and Pharmacoeconomics

Testimony of:

Aaron S. Kesselheim, M.D., J.D.

Assistant Professor of Medicine, Harvard Medical School

Division of Pharmacoepidemiology and Pharmacoeconomics

Brigham and Women's Hospital

Boston, MA

United States House of Representatives
Committee on Energy and Commerce
Subcommittee on Health
February 15, 2012
Washington, D.C.

1620 Tremont Street, Suite 3030, Boston, MA 02120 Tel: +1 (617) 278-0930 Fax: +1 (617) 232-8602
e-mail: akesselheim@partners.org http://www.drugepi.org/staff/faculty/faculty_akesselheim.php

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Summary of major points

- Approval of high-risk medical devices by the FDA can take longer than in the European Union when the FDA requires proof of safety and efficacy for clinical outcomes. In the EU devices, are usually tested to ensure safety and basic performance.
- The EU device approval framework resembles the pre-1962 US prescription drug market, when the FDA did not require companies to show that the drug had any clinical benefit for patients, so whether a drug worked was determined based on haphazard patient experience after the product was marketed.
- Legislation in 1962 requiring proof of efficacy for new prescription drugs helped spur the expansion of the pharmaceutical industry because physicians and patients could be more confident in drugs validated by the FDA, and companies were incentivized to develop useful new drugs to meet those standards.
- There are numerous examples of European patients being exposed to high risk devices later found to be ineffective, unsafe, or both, after clinical testing required by the FDA. US patients were spared from these bad outcomes.
- Even the most rigorous premarket testing by the FDA cannot identify all potential safety concerns, so active post-market surveillance of high-risk devices is essential.
- Patients and physicians want access to products that provide meaningful clinical benefits with a reasonable assurance of safety, and MDUFA should bolster the FDA's ability to meet these expectations by increasing funding for its essential functions and giving the FDA greater latitude to require and oversee rigorous post-market surveillance.

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Chairman Pitts, Ranking Member Pallone, and Members of the Subcommittee on Health:

My name is Aaron Kesselheim. I am an internal medicine physician in the Division of Pharmacoepidemiology and Pharmacoeconomics at Brigham & Women's Hospital in Boston and an Assistant Professor of Medicine at Harvard Medical School. I am also an attorney trained in patent law. My research focuses on legal and regulatory issues that affect use of prescription drugs and devices. It is an honor to have the opportunity to share my thoughts with you about the regulation of medical devices.

The essential question being addressed in today's hearing is whether requiring the FDA to loosen its standards for medical device approval and regulation would encourage innovation and provide patients with easier access to the latest technology. Some manufacturers, policymakers, and physicians offer the European Union as a model, providing statistics showing that high-risk devices generally make it to the market sooner and more easily in the EU.

The main reason for this disparity is that the EU device approval organizations, called Notified Bodies, usually require only studies in small numbers of patients showing the device appears to be safe and performs as expected. For example, such evidence could include demonstrating that a new stent expands appropriately in the coronary artery, or that a device for a left atrial appendage exclusion can be deployed as intended. There are no requirements in the EU that companies demonstrate that their devices benefit patients. By contrast, the FDA requires more robust evidence of safety and effectiveness for many of these implantable or high-risk devices. Thus, approval for this same coronary stent might require showing that it reduced cardiac events such as heart attack or the need for another invasive cardiac procedure. FDA

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approval of the left atrial appendage exclusion might require demonstration that the device not only be safely implanted, but reduces risk of stroke—the main reason for its use in the first place.

The current EU system for approving medical devices recalls the US prescription drug market before 1962, when the FDA only required limited studies of purity or safety before a drug could be marketed, and did not require companies to show that the drug had any real clinical benefit for patients. But after the thalidomide public health crisis, legislation gave the FDA authority to compel reasonable efficacy and safety data before a new drug could be sold. This reform was almost derailed by accusations that it would threaten the viability of the pharmaceutical industry.[1] But what happened instead was that the US pharmaceutical industry grew over the next decades into one of the most profitable in the world.

Why? A key contributor was the validation that the FDA now provided. Physicians could prescribe and patients could use drugs approved after 1962 with the confidence that a neutral, expert body had certified their efficacy and safety. Requiring companies to demonstrate that their products were effective also created an incentive for manufacturers to subject their product evaluation to a higher standard, leading to their developing some of the most important medications on the market worldwide. Today, no reasonable policymaker or drug manufacturer advocates returning the US prescription drug market to a time when we essentially let any product on the market and then figured out afterwards which ones were useful or dangerous based on haphazard patient experience.

But this is indeed what is happening now in the EU for approval of even the highest-risk medical devices. For example, the French company PIP is now under criminal investigation for using nonmedical grade silicone in its breast implants, and tens of thousands of women in the EU

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have been advised to have their implants removed.[2] PIP's silicone breast implants were never submitted or approved for marketing in the US. In an article published online yesterday by the New England Journal of Medicine, Daniel Kramer, Steve Xu and I describe some other cases in which EU patients were exposed to devices later shown in clinical trials to be ineffective, to cause substantial harm, or both, including[3]:

- The PleuraSeal lung sealant system, which was developed for the treatment of air leaks after pulmonary resection surgery. The PleuraSeal technology was approved in the EU in 2007. However, a clinical study conducted as part of an FDA premarket approval application showed in 2011 that the new technology had triple the rate of adverse events compared to standard techniques used to seal surgical incisions. As a result, the device was rejected by the FDA, and on the basis of these data, a worldwide recall was initiated.[4]
- The Acorn CorCap cardiac support device, a harness for patients with heart failure to improve their cardiac output. The device was granted EU approval in 2000, but subject to a pivotal premarket trial by the FDA. The approximately 300-person trial, completed by 2004, showed no change in mortality, and had numerous irregularities, including missing data for about 40% of patients. It was not approved by FDA.[5]

In these cases, FDA-required premarket testing helped identify unsafe or ineffective devices. But as more recent public health crises in the drug and device markets have shown,[6 7 8] the FDA approval process is not perfect. Even the most rigorous premarket testing cannot identify all potential safety concerns, and the FDA must use a "least burdensome" approach in

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working with manufacturers to decide what clinical data will be required, which places statutory limits on the extent of premarket device testing. The clinical trials submitted to FDA to support approved devices do not always use high quality methods, such as blinding, randomization, or robust endpoint definition.[9] [10] In addition, other experts have identified clearance of high-risk devices through pathways designed for lower-risk devices as an important inconsistency between the FDA's mandate and its practice;[11] the FDA is currently working to correct these situations.[12]

Thus, patient safety also mandates enhanced post-market testing of new devices. In the drug world, one of the lessons from the Vioxx episode was that safety surveillance cannot be dependent on the receipt of adverse event reports alone.[13] More active post-market device surveillance could include development of national registries with mandatory reporting of all implanted devices, along with automatic review of clinical experiences with certain devices after a period of years to ensure that they are producing the expected benefits. With today's advanced informatics and epidemiological surveillance techniques, this would not be a problematic requirement in terms of either cost or regulatory burden.

In summary, patients and physicians do not want access to *any* latest drug or device; rather, they want access to products that provide meaningful clinical benefits with a reasonable assurance of safety. This is what FDA approval ideally provides. Congress should use the Medical Device User Fee Act to bolster this essential role of the FDA—for example, by increasing funding for better inspections of manufacturers, hiring of more reviewers or safety experts, and by providing for more rigorous post-market surveillance—so that devices proven to be effective and safe can be used confidently by physicians for the benefit of their patients.

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