Testimony of Bruce M. Psaty, M.D., Ph.D.
Before the House Committee on Oversight and Government Reform
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Mr Chairman and members of the Committee,

My name is Bruce Psaty. I am a professor of medicine and epidemiology at the University of Washington. I wrote the NEJM editorials that accompanied Dr Nissen's meta-analysis and GlaxoSmithKline's RECORD trial (1-4). I also served on the IOM drug safety committee (5,6). This testimony reflects my professional views as a public-health scientist.

The crisis in confidence about the safety of medicines in America, which started with the withdrawal of rofecoxib in September 2004, sadly still awaits resolution. The problems raised by Avandia, the subject of the hearing today, point to the importance of several recommendations made by the IOM drug safety committee (5,6). The FDA needs the leadership and authority to require sponsors to conduct high-quality postmarket trials in a timely fashion. Public posting of clinical trial data was crucial to the identification of the heart-attack risk associated with Avandia. Direct-to-consumer advertising increases demand for drugs, some of which, like Avandia, may have been incompletely evaluated. The FDA needs additional resources, preferably from general revenues rather than PUDFA funds. Joint authority for regulatory actions in the postmarket setting is also essential for the Office of Surveillance and Epidemiology. Decisions about safety matters need to be turned over in part or in whole to new group with a more robust public health focus.

Dr Nissen conducted a meta-analysis, which is a method of summarizing the findings of previously conducted trials. In Dr Nissen's meta-analysis, Avandia was associated with a significant 43% increase in the risk of heart attacks. In other words, Avandia increases heart attack risk by about as much as the statin lipid-lowering drugs reduce heart attack risk.

The main limitations of Dr Nissen's meta-analysis were the quantity and quality of the available data. The responsibility for the limited availability of high-quality data resides with GlaxoSmithKline, which did not conduct studies to definitively address heart attack risk in a timely fashion. The regulatory history of Avandia includes several key missed opportunities.

Avandia was approved on the basis of its ability to lower blood glucose. Because high levels of glucose increase the risks of vascular disease, a glucose-lowering drug is presumed to reduce the risk of a heart attack. Paradoxically, Avandia appears to increase rather than decrease heart-attack risk.

GSK did not make a serious effort to verify the presumed health benefits of Avandia in a timely fashion. The ADOPT (7) and DREAM trials (8) focused largely on marketing questions and failed to address directly questions of heart-attack risk or

benefit.

For drugs that will be used by millions of people for many years, it is essential to document the health risks and benefits of new therapies approved on the basis of surrogate endpoints (9). Laboratory measures such as blood glucose must be converted into clinically meaningful outcomes (10). If sponsors do not voluntarily initiate large long-term trials of public health importance, then the FDA needs the authority to insist that they do so in a timely fashion.

In August 2006, GSK provided the FDA and the European Medicines Agency, the European equivalent of the FDA, with the results of several studies, including a meta-analysis (11) similar to Dr Nissen's. By October 2006, the product labels in Europe were revised to include this information (12). The US product label still does not identify heart attack as a potential adverse reaction in the general population of diabetics.

It is not clear why FDA failed to make this information public before Dr Nissen's meta-analysis was published. The primary measure of regulatory success is the timeliness of information, warnings, or withdrawals. With Avandia, FDA failed to warn or inform in a timely fashion.

GSK's RECORD study has several major limitations in design and conduct (4), and even if it continues to its planned conclusion, information about heart attack risk from the RECORD trial is likely to be incomplete. After incorporating the interim results of the RECORD trial into the meta-analysis, Avandia is still associated with a significant 33% increase in the heart-attack risk (4). The possibility of heart-attack benefit remains remote, and there is still statistically significant evidence of harm.

Late and incomplete evaluations of the health risks and benefits of drugs such as Avandia create confusion and uncertainty among patients, physicians, and policy makers. The House of Representatives, which is about to take up drug-safety legislation, has a unique opportunity to prevent future drug-safety problems and reinvigorate an essential regulatory agency that has many outstanding scientists.

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