STATEMENTS FOR THE HEARING RECORD OF
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COMMITTEE ON OVERSIGHT AND GOVERNMENT REFORM
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Mr. Chairman and Members of the Committee:

Thank you for inviting my testimony on the important question of the safety of Avandia, and the implications of this episode for national drug safety policy.

As introduction, I am George S. Pepper Professor of Public Health and Preventive Medicine, founding Chair and Professor of Biostatistics and Epidemiology, Professor of Medicine, Professor of Pharmacology, founding Director of the Center for Clinical Epidemiology and Biostatistics, founding Director of the Graduate Group in Epidemiology and Biostatistics, and Associate Vice Dean, all at the University of Pennsylvania School of Medicine. I am also Associate Vice President for Strategic Integration of the University of Pennsylvania Health System. My curriculum vitae is attached. I have spent my career investigating questions of drug safety. During the last few years, I have received funding from the Agency for Healthcare Research and Quality, the National Institutes of Health, the Pennsylvania Department of Health, Pfizer Inc., and Takeda Pharmaceuticals North America, Inc.; served on the Board of Medco Health Solutions, Inc.; received support for a pharmacoepidemiology training program from Amgen Inc., Berlex, Inc., Merck Company Foundation, Novartis Farmaceutica, SA, Wyeth Consumer Healthcare, Wyeth Pharmaceuticals Inc., and Pfizer Pharmaceuticals Inc.; served as a consultant to Abbott Laboratories, Aetna Health Management, LLC (Aetna Inc.), American College of Neuropsychopharmacology, AstraZeneca LP (AstraZeneca), Berlex, Inc., Biogen Idec Inc., Blue Cross Blue Shield Association, Bristol-Myers Squibb Company, Centocor Research & Development, Inc., Cephalon, Inc., CV Therapeutics, Inc., Cygnus Corporation, Inc., Daiichi Sankyo, Inc., Roche Laboratories, Inc. (Hoffman-LaRoche, Inc.), Oscient Pharmaceuticals Corporation, SmithKline Beecham Corporation (GlaxoSmithKline), Johnson & Johnson Services Inc., Lilly Research Laboratories (Eli Lilly and Company), Institute of Medicine of the National Academies, Novartis Pharmaceuticals Corporation, Pfizer Inc., Sanofi Pasteur Inc., Integrated Therapeutics Group, Inc. (Schering-Plough), Shire Development Inc., TAP Pharmaceutical Products, Inc., Warner-Lambert Company, and Wyeth Pharmaceuticals Inc., and served as an expert witness for law firms representing the Bayer Corporation, and plaintiffs suing pharmaceutical companies.

I will begin by discussing the scientific issues of Avandia safety regarding myocardial infarction, followed by the policy implications, and then provide some conclusions.

SCIENTIFIC ISSUES

Nissen Paper and Its Issues

As the committee is well aware, this latest "drug safety crisis" began with the publication of a paper by Nissen and Wolski, pre-released on the website of *The New England Journal of Medicine*, along with an accompanying editorial (1, 2). The design of the study raises a number of important issues. I will discuss each in turn.

Meta-analysis is an inherently weak and controversial design. The study used the technique of meta-analysis, a well recognized and potentially useful but sometimes controversial study design (3). It uses statistical techniques to add together diverse studies, on the assumption that they give a single answer, attempting to synthesize the studies statistically. However, it is widely acknowledged that it is far preferable to perform a single study with sufficient sample size to answer the question properly.

Most of the trials included were not peer reviewed. Most meta-analyses investigate published studies only. Indeed, meta-analyses normally struggle with the question of whether only selective information is available because of unpublished studies that are not available. In this meta-analysis, in great contrast, most of the studies included were unpublished. While this avoids the issue of publication bias, it raises other important issues, in that the underlying studies in this meta-analysis were never subjected to the usual criteria of scientific peer review. This leaves uncertain the quality of the underlying information.

Six trials were omitted because they did not report any myocardial infarctions or deaths. Most meta-analyses are performed to evaluate the effectiveness of a drug or other exposure. In the Avandia situation, of course, the meta-analysis was conducted to evaluate drug safety. When measuring drug effectiveness, normally all patients have an outcome. When measuring drug safety, in contrast, most patients fortunately do not have the outcome of concern. However, meta-analytic techniques are not equipped to deal with studies with zero outcomes. This necessitated the omission of six studies from the analysis. However, in a study of drug safety, zero outcomes is very meaningful, i.e., it defines the ultimate safety. The omission of such studies is likely to exaggerate any observed difference between the treatment group and control group.

There are marked differences among the studies, yet they are all being combined as if one would expect the same answer. Inherent in the technique of meta-analysis is the assumption that the studies are all giving the same answer. Yet, these studies are extremely different from one another, with different patient populations, and even different comparison groups. Some of the studies compared Avandia to placebo, while others compared Avandia to various other antidiabetic drugs. ***The largest study, by far, considered in the meta-analysis did not even include patients with diabetes***. Combining all of these studies into a single analysis is quite questionable.

These studies were not designed to study myocardial infarction; therefore, absent adjudication, we do not know if the cases of "myocardial infarction" truly had myocardial infarctions. It is conventional in a clinical trial to spend considerable effort to validate whether the people with the outcome in question truly had the outcome. Often, on more detailed exploration, it turns out they did not. This is certainly the case with studies of myocardial infarction, as this term is used liberally, often in patients who do not truly have it. Alternatively, cases of myocardial infarction could easily be missed, if this was not the purpose of the study. Thus, this makes the outcomes in such studies very difficult to interpret, at best.

The absence of patient-level data led to incorrect analyses, which did not adjust for duration of follow-up. The ideal meta-analysis obtains the actual data of the original studies, so that individual patients can be identified and analyzed accordingly. In this scenario, duration of patient follow-up can be adjusted for. If a patient is followed for three months, s/he has three times the risk of a patient followed for one month, independent of any exposure. It is critical that this be dealt with. The authors did not have individual-level data, but only study-level data. Accordingly, they could not apply such analyses, and the statistic used was the odds ratio rather than the hazard ratio, which should have been calculated. Further, to adjust for this, the authors restricted their meta-analysis to studies where the two treatment arms had the same duration of treatment. It is not clear how many studies were omitted in the process, and how this would have affected the results.

Borderline statistically significant findings. In this context, the authors' findings were only borderline statistically significant. The odds ratio for myocardial infarction had a p value of 0.03, while the odds ratio for death from cardiovascular causes had a p value of 0.06. These are very close to the conventional scientific cutoff of 0.05. This means that the findings of this meta-analysis could possibly be due to random error. Given then all of the problems listed above, it is easily conceivable that correction of such problems could have resulted in the association here disappearing entirely. Alternatively, of course, correcting these could result in the association getting stronger. One simply cannot know.

Other Data Are Available with Different Results

The nature of science is that one looks at all available data before making a decision. At the time of the release of this study, the FDA had access to two other studies, which have now been released publicly as well. The first is the RECORD study, a large clinical trial of the kind that needs to be mounted to answer this question definitively. The results are as yet preliminary, and underpowered (4). However, they do not support this concern. The second is a very large epidemiologic study including about 30,000 Avandia users (5). Thus, there is considerable statistical power. No increased risk was seen with Avandia. Of course, like all scientific studies, these are not perfect either. RECORD is as of yet, at least, underpowered, since we are presented only with an interim analysis. Other valid criticisms have been pointed out as well (6). The epidemiologic study is, inherently, non-experimental. The authors went through extreme efforts to make the groups as similar as possible. However, one cannot exclude systematic differences between the study groups, absent randomization. Once again, the only way to address this question definitively is a large, single, randomized trial. However, it is clear that these other two studies do not confirm the marginal findings of the Nissen paper.

Synthesis

In summary, it is clear that the Nissen meta-analysis was a very weak study. It has many problems, most of which were identified, described, and discussed by the authors. This is not a question of science conducted ignorantly, but conducted quickly. It is clear that the study raises an important question. However, it is exceedingly far from providing an answer to that question. Indeed, this is a question that had been raised well before this paper was published. The two other studies available so far do not support this finding, although they too are not definitive. The best way to address such a question is a large outcomes-oriented randomized clinical trial, and one is underway, i.e., RECORD. Ultimately, the hypothesis identified in the Nissen paper may indeed be proven to be correct, but it may not be.

Is there a proper long-term therapeutic role for this drug? To date, the available data regarding myocardial infarction are not substantially changed from the data available at the time of drug approval. We do not yet know the eventual answer about whether this drug should be used. A large outcomes study was needed at the time the drug was marketed. One is now underway. Premature regulatory action should not be taken in the absence of scientific knowledge. Indeed, while it is not clear whether the drug causes this side effect, it is clear that toxicity results from removing patients from drugs they are doing well on, and switching patients to new drugs. It would be most unfortunate if this overreaction also led to the compromise of the definitive study, RECORD, as then we would never have the answer.

POLICY IMPLICATIONS

Congress and the Public Need to Understand That No Drugs Are Safe

It is critically important that Congress and the public understand that no drugs are safe. This includes prescription drugs, over-the-counter drugs, and also nutritional supplements. Drugs are given to interfere with the body's systems. Thus, if they are effective, they will have side effects. In the case of prescription and over-the-counter drugs, we know that the drugs have benefits, felt by regulators to outweigh the inevitable risks. It does not mean these risks are absent. Indeed, it is ironic that we, as a society, panic over rare adverse effects from drugs known to have a beneficial effect, yet allow on the market nutritional supplements that also may have toxic effects, and have never been proven to have any beneficial effect whatsoever. It is critically important that the issues raised by Avandia be looked at in proper perspective.

Congress and the Public Need to Understand That the Discovery of a New Adverse Reaction After Marketing is Not Intrinsic Evidence of Someone's Failure

As a society, we study drugs after they are marketed in, generally, 2000 to 3000 patients. This means that adverse reactions that occur once per 100 patients will be known at the time of marketing. In contrast, adverse reactions that occur once per 1000 patients, or less commonly, will not be known as of the time of marketing. This is an intrinsic part of our drug approval process. The discovery of a rare adverse event after a drug is marketed does not mean that somebody necessarily failed in their job. To the contrary: someone succeeded, as the adverse event was detected. I worry more about all the safety problems we do not detect. To be more certain of drug safety at the time of marketing would not mean extending studies to 4000 or 5000 patients, but to 20,000 to 30,000 patients, or even 200,000 to 300,000 patients. These numbers simply are not attainable prior to marketing. Further, even if they were, such a requirement would dramatically delay access to good drugs to many patients who need them. It does mean, however, that considerable information will continue to emerge after a drug is marketed, and it behooves us to expedite this when is the drug is marketed.

The Risk/Benefit Balance of a Drug Continues to Evolve After Marketing

It also means that when the drug is first marketed, physicians, patients, and society need to take into account in making a risk/benefit judgment, the substantial probability of as yet unknown adverse reactions. To me, this argues to limit the marketing of a drug in its first years on the market

to those patients who truly need it, and to collect as much information as possible on their experiences, so that all can learn about uncommon adverse effects as soon as possible.

There Is a Critical Need for Outcomes Studies to Be Performed After Marketing

Many drugs are approved using studies that investigate the true purpose of giving the drug, e.g., drugs given for symptom relief. Other drugs, however, are given to achieve long-term outcomes that cannot practically be investigated prior to marketing. For these, we commonly investigate surrogate outcomes, expecting that the efficacy of the drugs on the surrogate outcomes will approximate their efficacy on true outcomes. In most cases this is borne out to be true. For example, anti-hypertensive drugs were approved for marketing on the basis of their ability to lower blood pressure, and many studies have since shown the many positive effects of these drugs on cardiovascular disease, stroke, etc. As another example, statins were approved for the market on the basis of their ability to lower cholesterol, and subsequent studies have clearly shown the long-term improvement of cardiovascular outcomes associated with their use. This is not always guaranteed, however. It is critically important that drugs approved on the basis of surrogate outcomes be accompanied by large-scale outcome studies conducted as soon as possible at the time of marketing so that this assumption can be tested.

There Is a Critical Need for Comparative Effectiveness Studies to Be Performed After Marketing

By law, drugs are approved on the basis of their safety and efficacy, i.e., do they work for a given indication and is their risk worth this benefit? This requires, with rare exceptions, studies comparing drugs to placebo, rather than studies comparing drugs to each other. Indeed, for good scientific reasons, this is generally a preferable approach, since it is then in the sponsor's interest to perform the best study possible to identify a difference from placebo, as opposed to conducting a sloppy study that will fail to identify a difference from an active drug. This approach is also often logical, since patients who respond to one drug in a class do not necessarily respond to other drugs in the class. Thus, some choice is of use. Nevertheless, it is a critical clinical question to identify the relative safety and efficacy of a drug, in comparison to others available for the same indication. This remains to be performed after marketing and, indeed, is rarely forthcoming.

There Is a Critical Need for Observational Studies to Be Performed After Marketing

In addition to the host of safety questions that often remain, and later emerge, at the time of drug marketing, pre-marketing trials are generally conducted in a select, artificial population, i.e., patients willing to be enrolled in clinical trials. It is critically important to find out what the true effects of a drug are when used in the general population, without the artificial protections and selections inherent in a clinical trial. This, along with the inevitable safety questions that emerge, demand use of epidemiologic, non-experimental study designs after drugs are marketed.

FDA's Credibility Is Critical to Protecting the Public's Health

If there is a plane crash and a small number of people die, we mobilize an expert organization to evaluate why this occurred, trust the results we obtain, and learn from the experience in order to prevent the next plane crash. In many ways, the FDA serves that role for society. Indeed, it receives hundreds of signals of possible adverse reactions each year, similar to

those that emerged from the Nissen paper. Its job is to evaluate those signals, decide whether more information is needed, and decide whether regulatory action is to be taken. When such a question is asked publicly, the public must be able to turn to the FDA to provide an answer. Poorly placed panic and accusations that hurt the FDA's credibility do not help the public's health, but rather harm it.

It Is Imperative That FDA Be Markedly Strengthened and Resourced to Address Such Issues Properly

The US drug safety system is indeed flawed, and should be changed (7). The problem, however, is not the actions of individuals or the FDA, but Congress. Congress has not seen fit to create a system that is rational. Right now, we have crying needs for studies conducted after drug marketing. Yet, the FDA does not have the regulatory authority to require such data, does not have enforcement authority if the data are not provided, and our pharmaceutical manufacturers are given no incentive whatsoever to provide it; quite the contrary. It seems hypocritical for Congress to criticize the FDA when it is doing the best it can with the limited authority and resources it was provided by Congress. I have previously published in the *Journal of the American Medical Association* a proposal for a drug safety system that makes more sense (7), and I will briefly summarize it here.

Conditional approval. First, when a drug is initially approved, it should enter a period of conditional approval. During this time, marketing, especially direct-to-consumer marketing, should be restricted. Conditional approval would be removed only when sufficient numbers of individuals have been investigated to ensure the detection of rare side effects and to answer all drug safety questions that emerged pre-marketing or thereafter. This way, drug use immediately after marketing would be restricted to those who truly need the drug, in whom the risk/benefit balance in the face of uncertainty is more favorable. In addition, sponsors would have an incentive to gather safety information quickly, instead of delaying such efforts.

Empowered FDA. Second, we need an empowered Food and Drug Administration. The FDA needs an increased ability to regulate drugs after marketing so that it can, for example, require post-marketing studies and labeling changes, rather than these studies and labeling changes being subject to negotiation. The FDA also needs markedly increased resources to conduct and fund more post-marketing safety studies. The Institute of Medicine's report on drug safety estimates that 10 safety signals per year could be evaluated extramurally at an annual cost of between $10 million and $60 million (8). Perhaps we need an additional $50 million, or maybe an additional $150 million, depending on how much safety the public seeks. However, these sums are trivial in comparison to the $188.5 billion that was spent on prescription drugs in the United States in 2004 and the $11.9 billion on pharmaceutical advertising in the same year (9). In contrast, the FDA's current extramural epidemiology contracts program has a budget of less than $1 million per year, to investigate <u>all</u> drugs (9). This is preposterous.

A complementary nongovernmental organization or organizations. Third, I would propose the need for a complementary nongovernmental organization or organizations for performing non-regulatory tasks that are not now, nor should be, the mission of the Food and Drug Administration. Among such tasks are attempts to change prescribers' use of drugs, including old drugs; performing post-mortem examinations in the event of drug "disasters"; developing new methods for doing such studies better; training new scientists in this field; and other such non-regulatory tasks. This body

should probably be a nongovernmental organization since many of these tasks are academic in nature. This is a possible role for the Centers for Education and Research in Therapeutics (10), the Institute of Medicine, or other existing or future organizations.

CLOSING

In closing, I am once again grateful to the Committee for being willing to hear my proposals. In my view, an exaggerated response to the recent Nissen paper is misguided. Ultimately, this study may be proven to be correct, but it may not be. This is simply a signal, and only better science will determine whether the signal is real. The FDA gets perhaps hundreds of these signals per year, and it is its job to sort through them and determine when the signal is real. To date, at least, the two available studies, flawed but probably better, do not confirm this finding.

However, this whole episode does have important policy implications. It is critically important that Congress and the public have a better perspective on the true nature of risks from pharmaceutical products. Drugs are not without risk, and the risk/benefit balance of a drug changes during its lifecycle. Thus, there is an enormous need for additional information to be obtained about the effects of a drug after drugs are marketed. We need to create a system that provides pharmaceutical manufacturers with incentives to provide this information, rather than disincentives. Only in this way will the information be obtained more quickly. Further, we need to dramatically empower and markedly increase the resources of the Food and Drug Administration, rather than ridicule and criticize the FDA. The public needs to be able to rely on the FDA as a neutral, scientific, credible source of information and unbiased judgment when these questions arise, as they will do with increased frequency. Only in this way will the pharmaceutical manufacturers be forced to provide the information that must be provided to the public.

I call on Congress to make use of the opportunity of this public misunderstanding to make significant changes in the FDA, strengthening it in the process.

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