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Before the Subcommittee on Agriculture, Rural Development,
Food and Drug Administration and Related Agencies

Thank you, Madam Chairwoman, and members of the Subcommittee for allowing me this opportunity to present testimony about what we need to do to improve decision-making by patients, clinicians and policy-makers about pharmaceutical products.

My name is Harlan Krumholz. I am the Harold H. Hines, Jr., Professor of Medicine and Epidemiology and Public Health at Yale University School of Medicine, where I am Director of the Robert Wood Johnson Clinical Scholars Program and Director of the Yale-New Haven Hospital Center for Outcomes Research and Evaluation. I am a practicing Cardiologist and an internationally-recognized expert in outcomes research, a field of investigation that involves practical research to guide clinical care and health care policy, as well as a member of the Institute of Medicine, the health arm of the National Academy of Sciences.

I am the author of the book *The Expert Guide to Beating Heart Disease: What You Absolutely Must Know* and have written or co-authored more than 500 articles, reviews, and editorials in peer-reviewed medical journals, including articles relevant to the topic today. In addition, I am currently leading initiatives under contract with the Centers for Medicare & Medicaid Services (CMS) to develop national measures for public reporting of hospital performance, promoting transparency about hospital quality through the use of rigorously developed, clinically-important outcome measures such as mortality and readmission rates for common causes of hospitalization.

While the focus of today's subcommittee meeting is on Avandia, or rosiglitazone, my focus is broader. The nation's experience with Avandia makes it abundantly clear that in order to improve public health and safety, we need to ensure that information from clinical trial research is available to make sound, reasonable decisions about the drugs and devices being evaluated and to improve communication of trial results among patients, clinicians, policy-makers, and drug manufacturers. I would like to touch on some of the opportunities I have identified that can lead towards improvement.

Background

In 2006, as a cardiologist and epidemiologist, I was asked for my expert opinion by plaintiffs in litigation against Merck related to Vioxx (rofecoxib). After extensive review of public and private documents, I spoke to the likelihood of Vioxx having caused adverse cardiovascular events among several individuals. This experience deepened my understanding of the clinical trial research process and many of the challenges facing regulators as they evaluate drugs for approval or for new indications. In particular, the challenge of making use of all available clinical trial data to better understand drug efficacy and safety.

The similarities in the stories of Vioxx and Avandia are remarkable.

This brings me to my first point: **ensuring that information from clinical trial research is available to make sound, reasonable decisions about the drugs and devices being evaluated**.

When the public's health is involved, patients, clinicians, and policy-makers must know what can be known about a drug. They must have access to all available clinical trial research for comprehensive analyses and the most complete understanding. We too often make inferences about drug safety based on inadequate data. In part, this situation occurs because we simply lack the appropriate studies.

In part, this situation occurs because not all clinical trial research is published. Moreover, not all data collected within a clinical trial is published, even when the main findings are. These data are rarely available for analysis by independent individuals or organizations. Because science is based on the fundamental ability to reproduce findings, re-analysis of data ensures that it reflects the truth, and cannot be done when the data are not available.

What is the analogy here? It is like your favorite baseball team keeping the results of some of their games out of the standings. Is the team doing well or not? If you are only seeing partial results, you will find it hard to know. If companies are not sharing all their data from the trials, we cannot know about the safety of their drugs.

As an example, Vioxx was approved for use in the United States in 1999. The following year, in 2000, a clinical trial published in the New England Journal of Medicine found that Vioxx increased the risk of heart attacks when compared with naproxen. However, the company disputed the significance of these results and the drug was not withdrawn from the market until 2004, after more clinical trial evidence had accumulated.

Was all information from clinical trial research made available to make sound, reasonable decisions about Vioxx?

The answer is no.

In the course of the litigation, our research group was granted access to all of Merck's internal clinical trial data, all of the raw data files, including many of their trials that were never published and information that never made it into public view. We conducted an analysis in which we combined the data from the studies over time, as the results became available – revealing what could have been known at various points in time. This approach is traditionally described as a cumulative pooled analysis.

We found that the increased cardiovascular risk associated with Vioxx when compared with placebo was evident very early in the accumulated evidence of clinical trial data. When data from all of the clinical trials were examined together, there was a strong suggestion of risk by the time of the New England Journal of Medicine publication, and the risk reached a high level of scientific certainty by 2001, four years before Vioxx was taken off the market.

Again, the similarities between Vioxx and Avandia persist.

Because of litigation, Avandia's manufacturer, GlaxoSmithKline, made available on a company website data it would not traditionally have published: summary information for all clinical research trials examining Avandia. Many of these trials had not been published in the peer-reviewed literature.

Without access to the raw data files, investigators from the Cleveland Clinic were still able to pool this summary information for analysis and identified an increased cardiovascular risk associated with the drug. Their analysis and those of others would have been much stronger – much more definitive – if the raw files had been available.

How can we ensure that information from clinical trial research is available to make sound, reasonable decisions about drugs and devices being evaluated or approved by the FDA?

Recommendations

First, we need to increase transparency in the clinical trial research process. As the FDA Amendments Act of 2007 (FDAAA) now requires that all summary-level results from clinical trial research be posted within 12 months of study completion, I would strongly recommend that the raw data files be made available as well. The raw data is required for the most accurate and rigorous evaluation, allowing an assessment of quality and validity and enabling standardization of the analyses across studies and direct calculation of pertinent outcomes, which will ensure the best possible understanding of the accumulated evidence.

Second, if concerns are raised by the manufacturer, or the FDA, or by outside investigators, I would strongly recommend an independent evaluation of the data and report by at least two groups of expert, non-industry-affiliated investigators so that the findings can be verified.

Finally, when concerns about drug safety are verified, I would strongly recommend that the FDA commission an independent and impartial panel of experts to review the analyses and provide a report to Congress, made available to the public, comprehensively detailing what is known about the drug's efficacy and safety.

Once the accumulated evidence is synthesized and determined, **we need to improve communication of trial results among patients, clinicians, policy-makers, and drug manufacturers**.

We need more effective ways of conveying information about what is known about the expected benefits and risks of drugs – particularly those with substantial safety concerns. Many patients assume that treating their diabetes will improve their outcomes by reducing their risk of many health problems, including heart attacks and heart failure. They would be surprised to learn that the opposite seems true.

I have published an opinion that patients deserve to know their options – as well as the clear risks and benefits associated with clinical strategies that are offered to them. I consider this to be true informed consent – and what every patient deserves. In our current system we have not achieved this type of clear communication about key information.

Importantly, as part of the recently enacted Patient Protection and Affordable Care Act of 2009, Section 3507 requires the addition of quantitative summaries of the benefits and risks of prescription drugs in a standardized format (such as a table or drug facts box) to the promotional labeling or print advertising of such drugs. The rationale is that this information will improve health care decision-making by clinicians, patients and consumers.

What would improved communication about Avandia discuss?

First, in terms of drug effectiveness, clinical trial evidence clearly demonstrates that Avandia lowers blood glucose levels, which we would expect to improve patients' management of diabetes. However, there is no clinical trial evidence that Avandia reduces the risk of heart attacks, a common adverse event for patients with diabetes, or improves survival.

Second, in terms of drug safety, pooled clinical trial data demonstrate that Avandia is likely to increase the risk of heart attacks and certainly increases the risk of heart failure, an equally dangerous event.

How clearly is this information being provided to patients? Are all patients who are taking Avandia aware of the known and probable risks of the drug? As I recently wrote in another editorial, I do not know why any clinician would prescribe a medication that is associated with such risk when so many alternative drugs are available on the market. So why does the drug remain among the most popular for diabetes?

Recommendations

We need to avoid drugs without proven clinical benefits and with proven risks. I strongly recommend that we clearly disclose to patients when we do not know if drugs have a beneficial effect . Patients need to be in a position to make a fully informed decision about taking a drug, which requires that they know not just that a drug lowers blood glucose levels, but actually lowers the risk of heart attack or death. Where there are no studies on the impact of the drugs on patients' lives – whether they help them avert adverse events – and live longer and better – then there needs to be clear disclosure in any promotional material.

These themes about transparency and communication are resonating throughout medicine. The efforts to improve quality of care are based on assumptions that data should be shared in order to provide a common understanding that will guide practice and policy. Such an approach is paying dividends in the area of quality of care; it can do so in drug safety as well.