Trends-in-Medicine

August 2007
by Lynne Peterson

Quick Pulse

Trends-in-Medicine
Stephen Snyder, Publisher
2731 N.E. Pinecrest Lakes Blvd.
Jensen Beach, FL 34957
772-334-7409 Fax 772-334-0856
www.trends-in-medicine.com

FDA Advisory Panel Says Avandia Risky but Should Stay on the Market

Gaithersburg, MD
July 30, 2007

On July 30, 2007, two FDA advisory committees, meeting jointly, voted overwhelmingly to keep GlaxoSmithKline's controversial diabetes drug Avandia (rosiglitazone) on the market, despite determining that it increases the risk of a heart attack. The FDA's Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee voted 20 to 3 that Avandia increases cardiac ischemic risk in Type 2 diabetics, but they voted 22 to 1 that, instead of pulling the drug, the FDA should require strong, new warnings, or black boxes, in the label.

The panel said there was not enough data yet to say that the only other FDA-approved PPAR-γ agonist, Takeda Pharmaceuticals' Actos (pioglitazone), is safer than Avandia, even though some FDA experts argued that it is safer. The panel left any comparison of Actos and Avandia for a possible future panel to determine.

The panel chair, Dr. Cliff Rosen, an endocrinologist from Maine, summarized the panel findings: "The committee felt relatively firmly that there was some risk associated with the use of rosiglitazone in certain diabetic patients, and that risk was translated primarily by the meta-analyses, confirmed by three independent groups – GSK, FDA, and Dr. Steven Nissen. The committee felt strongly there was some increased CV risk…but the short-term data may not translate to a long-term risk. The signal for an increased risk was there. There was a near unanimous statement that Avandia increased CV risk…Everyone except one person felt it should stay on the market with specific warnings…Though the panel didn't vote to take it off the market, there will be changes in the way this drug is promoted, the way patients know about the drug, and certainly how patients use it."

The controversy over Avandia started accelerating in May 2007, when Dr. Nissen (past president of the American College of Cardiology) and his colleague Kathy Wolski MPH published a meta-analysis of 42 controlled clinical trials of Avandia in ***The New England Journal of Medicine*** which concluded that Avandia increases the risk of myocardial infarction (MI) and perhaps cardiovascular (CV) death by 43%. GSK maintains that Avandia is safe, and its meta-analysis showed a 31% increased risk for Avandia (1.99% risk of MI with Avandia vs. 1.51% with comparators). The FDA did its own meta-analysis and found a 38% increase in the risk of cardiac ischemic events. The panel agreed there is an increased risk but didn't feel it was sufficient to deny the drug to patients.

The FDA itself was sharply and publicly divided when it came to Avandia's fate. On one side, the drug surveillance officials – Office of Surveillance and Epidemiology (OSE) – said that the drug should be withdrawn from the market. On the

other side, the new drug officials in the Office of New Drugs (OND) in the Center for Drug Evaluation and Research (CDER) – defending their original decision to approve Avandia – said that it is safe and should stay on the market until and unless data from ongoing long-term trials confirm the signal seen in the meta-analyses. OSE lost.

Some members of Congress have been concerned that OSE should be independent of CDER and OND. Will the panel's decision add fuel to that debate?

Dr. Robert Meyer, director of the FDA's Office of Drug Evaluation II in the Center for Drug Evaluation and Research (CDER), admitted there was a "fundamental disagreement within CDER on the conclusions that should be drawn on the data" and appeared to defend Avandia. Dr. Meyer said the panel sent "a clear signal of concern…and we heard that…as well as the advice that it stay on the market with caveats that we will take under serious consideration…There was a wide range of expertise on the committee – biostatisticians, endocrinologists, patient advocates, etc. – there were fairly unanimous recommendations." He said that he was satisfied with the panel's decisions.

Dr. David Graham of OSE had argued that Avandia offers no major clinical health benefit, confers no clear advantage over other oral anti-diabetic medications, has no unique advantage over Actos, and actually appears to be inferior to Actos on some intermediate outcomes. He estimated that there will be one excess case of serious coronary heart disease for every 114 patients treated with Avandia. His conclusion: "Rosiglitazone should be removed from the market."

FDA drug safety expert Dr. Gerald Dal Pan, director of OSE and Dr. Graham's boss, sided with Dr. Graham, saying, "When we look at the data, the benefit:risk profile of Avandia is not favorable…I recognize there is uncertainty on the MI risk of rosiglitazone and the limitations of meta-analyses, but the data point to an increased risk to patients taking rosiglitazone, especially when compared to placebo…I don't think the benefits outweigh the risks of rosiglitazone."

Reaction to the Panel Votes

Dr. Dal Pan did not appear discouraged by the panel vote. He said, "The reason for an advisory committee is to get input…I was emphatic about hearing what the advisory committee had to say…There was a pretty consistent view among advisory committee members about the risk…We don't differ much there. The recommendation to keep it on the market was with a lot of caveats…If it remains on the market with a lot of caveats, there will be a lot of information for people to make a decision."

However, Dr. Graham had this reaction: "You saw the tension. The advisory committee was planned by OND (the Office of New Drugs), the committee was selected by OND, and the questions were framed by OND. It is a difficult situation…It says dangerous drugs can stay on the market because the FDA doesn't demand adequate evidence that they are unsafe. There is a public health disconnect."

Normally, the FDA will withdraw a drug from the market without asking an advisory committee for its opinion. In fact, FDA officials said they didn't know of any cases where the advice of advisory committee had been sought prior to a withdrawal in the past. Dr. Graham said the FDA would not go against the panel's advice and pull the drug anyway.

GSK chief medical officer Dr. Ronald Krall was relieved with the panel's decision. He said, "We welcome this decision as positive for patients…The committee recognized…the importance of multiple treatment options. Diabetes is a progressive disease that exacts a terrible toll on its victims, and it is important that Avandia remain a treatment option for patients."

Takeda officials were quick to emphasize the differences between Avandia and Actos, emphasizing the "proven safety profile" of Actos with regard to CV disease. Dr. Mehmood Khan, president of Takeda Global Research & Development, said, "Short- and long-term studies, both prospective and observational...all have shown no evidence that Actos is associated with an increased risk of heart attack or stroke… Although drugs may be in the same class, they also can have different clinical effects due to differences in molecular structure."

After the panel votes, Dr. Nissen, chief of cardiology at the Cleveland Clinic and a non-voting consultant to the panel, said, "I'm satisfied with the decision. They affirmed overwhelmingly that there is an increased CV risk with Avandia. They voted for a strong warning to inform physicians…My concern is that a black box doesn't always accomplish what is intended. We will watch to see how quickly the FDA acts, how they word (the warnings), and how they disseminate the information. It needs to be prompt and clear."

However, if Dr. Nissen had been a voting member of the panel, he said he would have gone further than the panel did, "Having heard all of the evidence, my vote would have been to withdraw the drug." He conceded that it is difficult to get physicians on an advisory committee to vote to withdraw a drug, but he predicted that Avandia use will decrease after the panel decision, "The use of the drug will very likely be curtained as a result (of the panel meeting and any new warnings). I think we will see utilization patterns change." Dr. Nissen said that if GSK had submitted the data the panel saw on Avandia under a new drug application (NDA), he doubted it would have been approved, "It is hard to conceive the drug would be approved."

The big question is what patients and doctors will do. Will doctors continue to prescribe Avandia or opt for alternatives, such as Actos or Merck's Januvia (sitagliptin), the first DPP-IV inhibitor?

Asked what message physicians should take away from the panel votes, Dr. Rosen said, "There are reasons not to use this drug in certain Type 2 patients – people who have or are prone to CHF, those with significant CV disease, especially if they have been previously hospitalized for MI, and I'd be concerned about nitrate users – where we found a significant interaction – and long-term users of insulin who probably have more advanced disease. Physicians need to think twice before prescribing this medicine to those patients." Dr. Nissen said, "There will be new warnings for this drug. I would expect some real changes in the use of this drug."

When will the FDA make a final decision on what to do about Avandia? Dr. Douglas Throckmorton, deputy director of CDER, indicated it may not be soon, "There are a lot of complexities in this…We need to go back and chart that course, meet with the offices involved, see what is outstanding…We need to talk internally on how much internal work is needed first…Obviously, this is a high priority for the Center…and we want to move forward as quickly as we can…On labeling, there were a variety of options suggested, some including a black box, others suggesting contraindications…I don't think I heard unanimous voice on that…so we need to talk among ourselves on how to proceed on that." Dr. Meyer added that the decision to put a black box on Avandia and Actos was made before the panel meeting.

GSK's Perspective

GSK argued that Avandia is safe and effective, and an important alternative for the treatment of diabetes. The company said that:

- All three meta-analyses do not meet the criteria that define a robust meta-analysis.
- A comprehensive evaluation of ongoing trials, when they are completed, is necessary.
- Avandia is not different from metformin or sulfonylurea (SU) and does not increase the risk of CV mortality or all-cause mortality in diabetes patients.

Dr. Ronald Krall, senior vice president and chief medical officer, insisted that all three meta-analyses that have been done on the CV safety of Avandia fall short of the criteria that define a robust meta-analysis: Similar objectives, patient populations, primary endpoints, event definitions, and event numbers (usually 200). He said, "It has always been our view that all three analyses have substantial limitations and can only generate hypotheses." Dr. Krall also said that GSK's position is that the RECORD, ADOPT, and DREAM trials show no increased risk of MI with Avandia, "The number of MIs are small, the data inconsistent, and there is no overall evidence that rosiglitazone is different from other oral anti-diabetes agents. Importantly, (we) will share new data from a large epidemiological study that rosiglitazone is not different from pioglitazone (Actos)…And in larger outcomes studies, there are fewer strokes in patients treated with rosiglitazone."

GSK View of Meta-Analyses of Avandia RCTs

Meta-analysis	MI risk	CV mortality risk
GSK	59%	91%
FDA	50%	70%
Nissen & Wolski	43%	64%

Dr. Krall pointed to several on-going, long-term studies that will shed more light on the safety of Avandia:

- **ACCORD,** an NIH-sponsored trial of 10,251 Type 2 diabetics, with a primary endpoint of MACE.
- **BARI-2D (**also an NIH-sponsored trial) of 2,300 Type 2 diabetics with coronary artery disease. The primary endpoint is all-cause mortality.
- **VADT,** a VA-sponsored trial of 1,792 Type 2 diabetics. The primary endpoint is a composite of MI, CV death, CVA, CHF, PCI, amputation, and limb ischemia.
- **APPROACH,** a GSK-sponsored trial of 672 Type 2 diabetics. The primary endpoint is change in atheroma volume by IVUS.
- **RECORD,** a GSK-sponsored trial of 4,400 Type 2 diabetics.

Dr. Krall said, "Rosiglitazone (safety) is not different from metformin or SU…What should be the way forward? Rosiglitazone does not increase the risk of CV mortality or all-cause mortality in diabetes patients. We need to also remember that the other anti-diabetic drugs show an increase in CV events in short-term studies, the mechanism and magnitude of which today are unknown and unexplained. We need to acknowledge rosiglitazone has the most comprehensive safety database of oral anti-diabetic drugs. We know more about rosiglitazone's safety in general than most currently available drugs. And we have five ongoing trials that will read out in the next 18-24 months and undoubtedly alone or as a group help us resolve any current uncertainty about the risk of MI associated with the use of rosiglitazone."

Saying that none of the available drugs for diabetics is perfect, but all are important, Dr. Krall described Avandia as an important choice, and he urged the FDA to wait for ongoing clinical trials to shed more light on the CV safety of Avandia.

GSK's vice president of clinical development, Murray Stewart, concluded, "There was no increase in myocardial ischemia in the long-term comparator study (ADOPT)…(And) there was no difference in reporting for events of myocardial ischemia in AERS (the FDA adverse event database) for either rosiglitazone or pioglitazone." He presented both GSK's view of the safety of Avandia in GSK trials and in insurance databases, concluding, "Studies of over 1.35 million diabetic patients have shown the risk of MI is similar for rosiglitazone to other anti-diabetic agents, and the risk of MI is no different between rosiglitazone and pioglitazone. The number of MIs in the clinical trials is small, the data are inconsistent, and

there is no overall evidence that rosiglitazone is different from the other oral anti-diabetic agents."

Stewart also stressed that fewer strokes were observed in Avandia patients, and Avandia is not associated with any increase in cardiovascular (CV) or all-cause mortality.

GSK Analysis of Avandia Safety

Measurement	Avandia rate per 100 patient-years	Comparator rate per 100 PY	Hazard ratio
Myocardial ischemia			
GSK integrated clinical trial (ICT) analysis (meta-analysis)	4.13	3.18	1.31
ADOPT trial	2.14	2.26 metformin 1.93 SU	0.99 1.93
Myocardial infarction (MI)			
ICT	1.09	0.75	1.59
RECORD	0.52	0.45	1.16
ADOPT	0.48	0.41 metformin 0.33 glyburide	1.23 1.52
DREAM	0.12 monotherapy 0.26 with ramipril	0.07 ramipril 0.14 placebo	0.83-1.85
MI plus sudden death			
ICT	1.09	0.75	1.59
RECORD	0.52	0.45	1.16
ADOPT	0.48	0.41 metformin 0.33 glyburide	1.23 1.52
DREAM	0.12 monotherapy 0.27 with ramipril	0.07 ramipril 0.14 placebo	0.83-1.85
Stroke			
ICT	0.31	0.67	0.48
RECORD	0.35	0.46	0.76
ADOPT	0.26	0.35 metformin 0.28 glyburide	0.77 0.94
DREAM	0.12 monotherapy 0.05 with ramipril	0.05 ramipril 0.07 placebo	0.67-1.66

GSK's Epidemiology Studies of Avandia Safety

Managed care database	Number of diabetes patients	Avandia MI rate	Actos MI rate
IHCIS	891,901	1.02 OR	0.90 OR
Ingenix	33,363	0.80/100 PY	N/A
PharMetrics	402,845	0.46/100 PY	0.37/100 PY

THE FDA PERSPECTIVE

Dr. Mary Parks of the FDA's Division of Metabolism and Endocrine Products explained that diabetes is "not some obscure medical disease." She also emphasized that interpretation of the data from all the different meta-analyses is complicated by issues involving statistics, trial design, patient populations, other risk factors, duration of exposure, and the complexity of the disease. Dr. Robert Ratner, vice president of scientific affairs at MedStar Research Institute and an Avandia defender, provided an overview of current diabetes treatments. He called diabetes "a prevalent disease, a growing disease, and an expensive disease" that requires a broad range of drugs to treat. He said that Hb_{A1c} is the only surrogate to see how we are doing with microvascular complications, but Hb_{A1c} is a good biologic correlate to microvascular disease complications. For each 1% reduction in Hb_{A1c}:

- The risk of microvascular complications drops 37%.
- The risk of fatal and non-fatal MI drops 14%.
- The risk of fatal and non-fatal stroke is reduced 12%.

An FDA statistician gave several reasons why the FDA did its own meta-analysis:

- GSK's analysis was an overall estimate for total MI events only.
- There was a suggestion of subgroup differences in the GSK analyses.
- There was heterogeneity among the different treatment paradigms.
- No results by individual studies were shown by GSK, and their analyses were not stratified by study.

The FDA meta-analysis included 42 randomized, controlled trials, all of which were double-blind, and it included patient-level data. The key findings were:

- A statistically significant overall estimate of a non-serious or serious MI event associated with Avandia: OR 1.4 (p=0.02).
- No evidence of increased MI risk with Avandia compared to metformin or SU: OR 1.0 (p=0.3).
- Increased MI risk with Avandia vs. placebo. Those results are heterogeneous across treatment paradigms/ studies and across subgroups.

FDA Analysis of CV Mortality + MI + Stroke (MACE) with Avandia

Trial	MACE HR	CV Mortality HR	MI HR	Stroke HR	TZD all-cause mortality
Pooled short-term studies	1.2 (p=0.4)	1.7 (p=0.2)	1.5 (p=0.1)	0.6 (p=0.1)	---
ADOPT (Avandia vs. SU)	1.2 (p=0.3)	0.6 (p=0.4)	1.6 (p=0.2)	0.9 (p=0.9)	0.8% Avandia vs. 1.4% SU and 1.0% metformin
ADOPT (Avandia vs. metformin)	1.1 (p=0.6)	1.3 (p=0.7)	1.3 (p=0.4)	0.8 (p=0.5)	
DREAM (Avandia vs. placebo)	1.1 (p=0.1)	1.0 (p=1.0)	0.8 (p=0.8)	1.7 (p=0.7)	1.1% Avandia vs. 1.3% placebo
DREAM (Avandia + ramipril vs. ramipril)	2.0 (p=0.1)	1.4 (p=0.6)	3.7 (p=0.3)	1.0 (p=1.0)	
RECORD	0.97 (p=0.83)	0.83 (p=0.46)	1.16 (p=0.50)	N/A	3.3% Avandia vs. 3.6% metformin/SU combination

Large thiazolidinedione (TZD) trials

A medical officer in the FDA's Division of Metabolism and Endocrinology Products gave an overview of the large prospective TZD trials. She said that:

ADOPT:

- Has not detected a significant difference in MI event rates between Avandia and metformin or SU.
- Cannot rule out a difference in MI risk.
- Showed a higher rate of heart failure events with Avandia than SU.

DREAM, though the FDA has not received all the data from this trial yet:

- Total mortality equal for Avandia and non-Avandia patients.
- Numerically more CV composite (macrovascular + heart failure) events for Avandia.
- Significantly more heart failure events for Avandia.

RECORD interim data:

- No increase in death or CV hospitalization (with or without heart failure) with Avandia.
- An increased risk (HR 2.24) of heart failure with Avandia.
- All-cause mortality and CV mortality not increased.
- Acute MI increased (HR 1.7, p=0.50).

PROactive study of Actos:

- No difference in CV mortality for Actos vs. placebo.
- No statistically significant difference in all-cause mortality – MI + stroke for Actos vs. placebo.

Safety

OSE's Dr. Graham said the benefits of Avandia do not outweigh the risks. He said he was expressing his own view, "But I am authorized to say that (my boss) worked closely with me and fully endorses, supports, and agrees with our methods, analyses, recommendations, and conclusions, but it is not an office position because he has not consulted with everyone on our team. But this is not just David Graham, FDA whistleblower, talking."

Dr. Graham raised three questions that he described as critical to determining the risk:benefit profile of Avandia, saying that if the answer to any of these questions is yes, then the risk:benefit profile of the drug has to be questioned:

1. ***Does Avandia increase the risk of CV events, most importantly cardiac death, AMI, and stroke?***

   Yes. He said:

   - The FDA meta-analysis shows 20%-68% increased risk with 6-12 months of Avandia use compared to non-use, which is especially noticeable in the placebo-controlled studies.
   - The DREAM trial shows ~40% increased risk with Avandia in a relatively low risk population. He said, "There is uncertainty about what the possible ACE inhibitor 'interaction' findings mean, but the CV risk is increased."
   - In DREAM, CHF was 0.8% with Avandia + an ACE inhibitor vs. 0.1% with an ACE inhibitor alone.

2. ***Does the CV risk with Avandia differ from that with Actos?***

   Yes. He said, "While (the existing Takeda meta-analysis) may not prove definitively that pioglitazone reduced CV risk, it certainly is not increasing the risk, and if anything, it looks like it may be decreasing the risk."

   - In DREAM, Avandia increased the risk by ~40%, while in PROactive, Actos decreased risk by ~15%.
   - In the Avandia meta-analysis, Avandia increased the risk of serious IHD by ~40% while in the Actos meta-analysis, the risk was decreased by ~25%.

3. ***Does the CV risk of Avandia differ from that of other oral anti-diabetic agents (e.g., metformin or SU)?***

   Unknown. The data provide inadequate and insufficient evidence to conclude that Avandia does not increase CV risk compared to metformin or SU. Neither RECORD nor BARI-2D will provide meaningful answers to this question.

Dr. Graham said the ongoing clinical trials of Avandia will not definitively answer the safety questions about Avandia, and he estimated that waiting for those trials would result in 1,600-2,500 adverse CV events per month in the interim. He concluded, "Are there definitively documented population-level health benefits of rosiglitazone to justify its continued marketing? No. Rosiglitazone should be removed from the market." He added, "Rezulin (Warner Lambert's troglitazone) was pulled from the market because of 80 case reports of acute liver failure. When that (Rezulin) was compared to pioglitazone and rosiglitazone, that same signal was not seen. At the time of the Rezulin withdrawal, the rationale was that Rezulin was an outmoded drug compared to pioglitazone or rosiglitazone. I think the same could be said about rosiglitazone today being compared to pioglitazone."

Dr. Meyer emphasized that he wanted the FDA's final decision to be based on a "good and fair evaluation of the data." He addressed the three types of evidence that the panel had to consider in weighing the FDA's questions:

1. **Meta-analyses.** "The most robust signal with rosiglitazone comes from meta-analyses…These have all the limitations of large RCTs – and more."
2. **Observational studies.** "We should not dismiss these out of hand."

3. **Individual RCTs**. "These don't show a worrisome signal. Some (people) in and outside FDA have the opinion that the RECORD trial won't have adequate statistical power to refute the meta-analysis signal…Many, myself included, find the (RECORD) data quite informative to date. On the composite of death, MI, and stroke, the point estimate for HR with rosiglitazone in RECORD is 0.96… While this may not prove the meta-analysis wrong, RECORD already has more outcome events than all the studies that made up the meta-analysis, and it already excludes a 25% increase in risk."

Comparison of FDA Analyses of Avandia Safety

Measurement	FDA meta-analysis	FDA review of longer-term trials
MI event risk	Significant increased risk for total MI events composite	Total MI events not significantly increased

PUBLIC WITNESSES

The public witnesses were overwhelmingly in favor of keeping Avandia on the market.

- **Gail Brashers-Krug**, speaking on behalf of ***Voice of the Diabetic*** magazine, urged the panel not to recommend withdrawal of Avandia, "Rosiglitazone is an essential part of the diabetic regimen for millions of Americans… Anything that makes it unavailable is likely to have the effect of worsening (patients') diabetes, which will likely mean worse complications."
- **Raul Fernandes**, vice president of The Mended Hearts, a non-profit organization for heart disease patients/ families, and himself a diabetic, said, "We feel that the decision to use medications should be made between the patient and his or her healthcare provider…It is vital that patients have as many tools in the toolkit as possible."
- **Department of Defense** military healthcare program (Tricare) speakers said they tracked 232,000 of their enrollees over four years (2003-2006) and found no increase incidence of CV events (acute MI and CHF) with Avandia, "Our big net did not find any outliers."
- **Dr. Sam Nussbaum**, executive vice president and chief medical officer of WellPoint, the largest managed care organization in the U.S., said they did a health outcomes study from five of their health plans and found no evidence for an increase in risk for either AMI or unstable angina in patients taking either Avandia or Actos. This was a retrospective, longitudinal cohort study of 22,060 Avandia and 23,768 Actos patients.

Wellpoint Analysis of Avandia Safety

Measurement	Avandia	Actos
AMI incidence rate	0.73	0.74
AMI HR	1.029	1.044

- **Richard Ralston**, executive director of Americans for Free Choice in Medicine, criticized members of Congress for interfering in the drug review process, and he criticized investigators who "manipulate" the system for their personal objectives.
- **Dr. Jerome Tolbert**, a New York City endocrinologist, said, "In my opinion…Avandia is a medication we need to help fight this disease. We need drugs of all classes to fight this disease. Avandia is not a perfect drug, but it is extremely useful and effective…Avandia has allowed me to gain control of many patients when I was otherwise unable to do so…Avandia has been a great help to me in treating my diabetic patients."
- **Dr. Bruce Trippe**, an endocrinologist with >2,000 patients on Avandia – and a big user of both insulin pumps and inhaled insulin, had his statement read into the record in his absence. The statement said: "Rosiglitazone is protective, not problematic."
- **J. Rick Turner, PhD**, a pharmacologist at Campbell University and president of Turner Medical Communications, commented, "The ***New England Journal of Medicine*** article (Nissen meta-analysis) is like a rubber mallet that has been given the weight of a sledgehammer."
- **Dr. Farhad Zangeneh**, an endocrinologist at George Washington University, said, "Every day in my practice we get phone calls about the ongoing issues surrounding TZDs…This needs to stop…In ADOPT and DREAM there appears to be no increased risk of ischemia. The DSMB of RECORD and BARI-2D are recommending these studies continue unchanged...I know TZDs have side effects, and the absence of side effects doesn't confer safety…The last thing people with diabetes…need to be concerned about is confidence in their medications…This resembles a soldier during a battle who has to question the integrity of his armor or the accuracy of his guns."

However, there was a vocal minority who argued that Avandia should be taken off the market.

- **Dr. David Eligman** of Brown University pointed out that European regulators – but not the FDA – have contra-indicated Avandia in patients with cardiac failure, "A black box is not enough…If this were an NDA, it would be rejected. Avandia has got to go until safety is adequately tested."
- **Dr. Sid Wolfe** of Public Citizen's Health Research Group said, "Our answer to the question, 'Does the overall risk:benefit profile of Avandia support its continued marketing in the U.S.?' is clearly no. There is no evidence of any uniquely beneficial clinical outcome for Avandia, and there is growing evidence in multiple organ systems – cardiac liver, bone, bone marrow – of unique risks. If this drug were up for approval today, based on what is now known, it would be summarily rejected.

There should not be a double standard for removing it from the market. Public Citizen is currently preparing a petition to the FDA to ban Avandia." Among the problems with Avandia, Dr. Wolfe pointed out, are liver failure, heart failure, bone fractures, and worsening of macular degeneration.

Two speakers simply urged the panel and the FDA to make a fair and informed decision.

- **Dr. Richard Hellman**, president of the American Association of Clinical Endocrinologists, said, "The problem highlighted by rosiglitazone is not unique. It is a system problem – the shortcomings of our national post-approval drug safety surveillance."
- **Charles Steele**, a 61-year-old diabetic, said, "Whatever your decision is, it will be fine with me as long as it is a fair decision."

PANEL DISCUSSION AND VOTES

The panel discussion and questions for the FDA prior to consideration of the FDA's formal questions focused on:

- Statistical methodology.
- Whether the Actos data should be considered or compared to Avandia since the Actos data presented have not been fully reviewed by the FDA yet.

Asked how to respond to public witnesses who urged the FDA not to take a tool out of physicians' toolboxes by withdrawing Avandia from the market, the FDA's Dr. Dal Pan said, "I recognize the burden of diabetes in the U.S. and the need for glycemic control and treatment, but if the risk of CV disease or excess MI is 40% above the background, this is something we would take very, very seriously. CV disease being the leading cause of death among diabetics, to have a treatment that does that, is something that just didn't make sense to me." FDA safety expert Dr. Graham added, "We could use much more effective therapies for diabetes, but at the end of the day, how many people does rosiglitazone keep out of the hospital or out of the cemetery because of coronary heart disease risk? And how many people is it putting into the hospital or a cemetery because of coronary heart disease?...It looks like there is no evidence it is keeping people out, and there is a substantial body of evidence that it is putting them in."

Other comments included:

- *FDA official:* "I would like the committee to grapple with this: There is not a whole lot of precedent to thinking of the level of statistical significance that should be attached to an exploratory finding even if it is a safety issue."
- *Dr. Graham (FDA):* "At some point you (panel members) have to make a decision on data that is not perfect. You have to make a decision based on what makes sense…We are in a situation where we don't have a definitive answer …but when I look at the totality of the evidence, I see repeated consistency with the bulk of the confidence intervals and point estimates pointing to increased cardiac risk and no evidence of major clinical benefit with rosiglitazone…If there is a reasonable chance you are causing harm, and there is no evidence of benefit…and there is an alternative, then why do you want to give rosiglitazone to anyone?"
- *Another FDA official* said that she is most confident with the subgroup analysis pointing to harm in Avandia patients also on insulin.
- *Dr. Nissen:* "The FDA did its meta-analysis one way and got a 40% increased CV risk with Avandia...We did it another way and got a 40% increased risk...GSK did it a third way and got a 31% increased risk. No matter how you cut the data, you get this 30%-40% MI (increase with Avandia)."

QUESTIONS 1-3 combined. Please comment on the contribution of the meta-analysis of the 42 controlled clinical trials as well as the observational cohort studies and the large randomized controlled trials (e.g., strengths and limitations) to the understanding of cardiac ischemic risk for Avandia.

Comments on observational studies:

- *Industry representative:* "I think the observational studies are not getting the credit they deserve."
- *Dr. Curt Furberg of Wake Forest University:* "I don't find the observational studies helpful at all."
- *Dr. Judith Fradkin, director of diabetes, endocrinology and metabolic diseases at NIH:* "We are talking about long-term disease…and it is the long-term effect that is going to make the difference for patients. I'm very uncomfortable by the inadequacy of the data we have…I thought we had pretty strong data from the observational studies."
- *Dr. John Teerlink, a UCSF cardiologist:* "I won't say observational studies aren't worth anything, but they don't inform my decision very much."
- *David Oakes, PhD, a biostatistician from the University of Rochester, who participated by telephone:* "Any conclusions we make are on short-term risk…Observational have the potential to detect very large effects, but they may not be able to detect the more modest effects we are talking about here."

Meta-analyses comments included:

- *Dr. Katherine Flegal of the Centers for Disease Control and Prevention (CDC):* "I'm concerned about the quality of the meta-analysis data, statistical issues, power, etc…I think there are still a lot of issues these studies don't answer fully."

Comments on randomized clinical trials (RCTs) included:

- *Dr. Judith Kramer, a pharmacologist from Duke:* "My sense is there is the usual tension between the desire to pinpoint exactly the effect of the drug…vs. answering the question clinicians need to know...We all know the limitation of real-world studies, but there are also advantages, and these (RCTs) were as well done as could be done."
- *Timothy Lesar, a PharmD from Albany Medical Center:* "The RCTs don't refute the meta-analysis."
- *Dr. Allison Goldfine, an endocrinologist from the Joslin Diabetes Center:* "We are unlikely to get the long-term data we need from ongoing studies…which leaves us the observational studies, which are problematic, though carefully performed…What is missing from them is out-of-hospital event rates."
- *Dr. Morris Schambelan, an endocrinologist from UCSF:* "I think the data could be more robust, but we are left with what is there…I'm concerned about the ongoing long-term studies being underpowered, so we will be left in a bit of a quandary…I'm concerned with throwing out the class or accepting data on another drug in the class (Actos) that was not reviewed as carefully as rosiglitazone…because I think the TZDs are very useful drugs."
- *Dr. Teerlink:* "RCTs are a gold standard, but the problem is none of them studied the patients I'm interested in; they all actively excluded the patients we are interested in. I don't see a signal in the RCTs, but that doesn't necessarily inform my decision about what to do about he drug as a whole."
- *Dr. Arthur Moss, a cardiologist from the University of Rochester:* "On RCTs, I'm intrigued that everyone comments that they won't show anything…I think the FDA can place much greater demand on gathering much more complete information, especially if we want to collect different endpoints."

QUESTION 4. Do available data support a conclusion that Avandia increases cardiac ischemic risk in Type 2 diabetes mellitus?

Yes by a vote of 20 to 3. The three no votes were Dr. Arthur Moss (cardiologist), Dr. Timothy Pickering (cardiologist), and Dr. David Schade (endocrinologist).

Panel members' comments on Avandia safety included:

- *Dr. Jessica Henderson, an associate professor of physical education at Western Oregon University:* "Despite the limitations of the data, I feel confident enough that there is a higher risk of CVD with Avandia, but I would want more data, especially long-term data and subgroups, especially patients on insulin and older patients."
- *Ruth Day, PhD, director of the Medical Cognition Laboratory at Duke:* "My concern is that we won't address the risk management issues…The sponsor's risk management plan was quite underwhelming."
- *Nancy Geller, PhD, an NIH statistician:* "I would like to see the FDA have more rigorous requirements for follow-up even if they do continue to approve diabetes drugs on the basis of six-month data."
- *Rebecca Killion, a patient representative:* "My primary concern is we are being asked to take a very draconian action based on studies with significant weaknesses that are inadequate for us to make that kind of decision."
- *Dr. Eric Holmboe of the American Board of Internal Medicine:* "I hope the FDA will consider a registry approach."
- *Dr. Rosen, the panel chair:* "We have a strong signal from three independent (meta-analysis) groups – Dr. Nissen, the sponsor, and the FDA – so it does suggest there is increased risk…On observational data, we have to be extremely cautious…We have been misled on a number of instances."
- *Dr. Timothy Pickering, a cardiologist from Columbia University Medical Center:* "A lot depends on a very small number of events…No one has provided any significant findings that there are increased deaths from patients taking rosiglitazone…My conclusions is (the data are) suggestive but by no means conclusive."
- *Dr. David Schade, an endocrinologist from the University of New Mexico:* "We absolutely as diabetologists, need a TZD on the market, and if we remove Avandia for what I consider a borderline data indication and in 1-2 years we find pioglitazone causes bladder cancer or something else, we will all look back and say, 'Gee, why did we do this?'…To perform a draconian action on this medication (Avandia) probably would not be advised in the long run."
- *Gerald Van Belle, PhD, a biostatistician from the University of Washington:* "Care has to be taken in who gets this drug…but the absolute risk is very small…On balance, we need to take that into account (when considering use of Avandia)."
- *Dr. Teerlink:* "There is no such thing as a perfectly safe drug…I think we see an overall higher risk (with Avandia)…There is information that sicker patients have a higher risk, patients on nitrates do worse, patients on insulin do worse…I won't say observational studies aren't worth anything, but they don't inform my decision very much…RCTS are a gold standard, but the problem is none of them studied the patients I'm interested in; they all actively excluded the patients we are interested in. I don't see a signal in the RCTs, but that doesn't necessarily inform my decision about what to do about the drug as a whole."

- *Dr. Lewis Nelson, an emergency medicine doctor from New York University Hospital Center:* "I'm concerned with the focus on relative vs. absolute risk."
- *Arthur Levin, the consumer representative:* "As a consumer advocate, I guess I believe in the precautionary principle which says when you have an indication of a problem, you have to have evidence that the problem is ***not*** there to decide what to do rather than a certainty that the problem exists."

QUESTION 5a. Does the overall risk:benefit profile of Avandia support its continued marketing in the U.S.?

Yes by a vote of 22 to 1. The negative vote was by the patient representative.

QUESTION 5b. Please comment on what FDA should do to maximize the risk:benefit considerations (e.g., limit to certain patients, incorporate a boxed warning, etc.).

More data and stronger warnings.

Generally, panel members thought that more data are needed on Avandia. They also called for a warning – but not a contraindication – for patients on insulin, on chronic nitrates, with prior CV disease. However, panel members did not agree on whether these should be prominent warnings or black boxes. The FDA has already announced that a black box warning for congestive heart failure (CHF) is going on both Avandia and Actos. Comments included:

- *Dr. Fradkin on the insulin warning:* "I wouldn't make it a contraindication."
- *Dr. Kenneth Burman, an endocrinologist at Washington Hospital Center:* "I'd like to see a warning and a black box for certain indications, including CHF, insulin, severe coronary heart disease, and use of nitrates."
- *Dr. Day:* "We really need better data, and the only way I think we can get that is a registry."
- *Dr. Geller* called for black box warnings.
- *Dr. Holmboe:* "Use should be restricted to a registry."
- *Dr. Peter Savage, an NIH epidemiologist:* "There needs to be a stiffening of the warnings…The signal with insulin is the most worrisome, but nitrates are a concern, too."
- *Dr. Nelson:* "I'd like a registry but that will be difficult and would eliminate most use…Perhaps there is another alternative…maybe more oversight from the FDA."
- *Dr. Teerlink:* "I suggest we remove the indication for insulin, and put on a black box warning that includes the issues of heart failure, patients on insulin, symptomatic coronary artery disease, and patients requiring nitrates."

Will there be another advisory committee on Avandia and/or Actos in the future? FDA officials left the door open for that.

♦