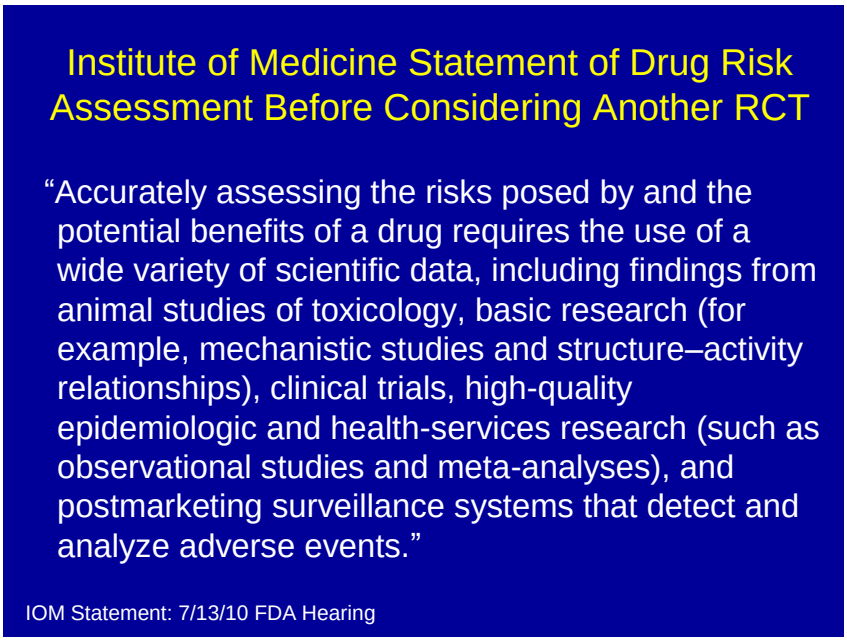
Testimony of Sidney Wolfe, MD, Director, Public Citizen Health Research Group
Institute of Medicine Committee on Ethical and Scientific Issues
in Studying the Safety of Approved Drugs
November 9, 2010

Thank you for the invitation to discuss ways to improve the evaluation of the safety of drugs after they have been approved in the face of safety signals that arise. I will discuss the questions you have put forth, with special emphasis on question five, How should FDA factor in different kinds of safety evidence in considering different kinds of regulatory actions?

1. What are the ethical and informed consent issues that must be considered when designing randomized clinical trials to evaluate potential safety risks?

The Institute of Medicine Committee's answer to FDA's question about what circumstances would justify a randomized controlled trial to examine the extent of danger of a marketed drug such as rosiglitazone are similar to the circumstances that should allow the continued marketing of such a drug:

If the previous knowledge about the drug's dangers is clear enough (in excess, compared to its benefits), the trial would not be ethically or medically justified. By the same logic, the FDA would need to remove the drug from the market because its overall risk-benefit profile would not support its continued marketing.



2. What are the strengths and weaknesses of various approaches, including observational studies, including patient registries, meta-analyses, including patient-level data meta-analyses, and randomized controlled trials, to generate evidence about safety questions?

The hierarchy should be RCT (see below about post-marketing RCTs for safety), patient level meta-analysis, meta-analysis, observational epi studies such as ICES or Medicare large population-based cohorts, case-control studies. However, the the point at which to enter this hierarchy depends on the nature and strength of the original safety signal (AERS report or epi study) and the uniqueness of the adverse effect (hepatic toxicity vs myocardial infarction) to determine what the follow-up study, if any, should be.

The most common reasons for drug safety withdrawal/black box warning actions are based on case reports derived from the AERS system, after carefully doing a Virchow-like analysis to rule out other potential causes.

3. Considering the speed, cost, and value of studies, what types of follow-up studies are appropriate to investigate different kinds of signals (detected pre-approval or post-marketing) and in what temporal order? (see answer to question 2)

4. Under what circumstances should head-to-head randomized clinical trials for safety be required?

In most, if not all, cases, if there is enough evidence of safety concerns from non-RCT sources to seriously consider the possibility of an RCT, the study would be unethical. This is especially true in the vast majority of such cases in which the drug has no unique evidence of life-saving/life-improving properties superior to other, less dangerous drugs. In many of these cases, these previous concerns should lead to at least a new black box warning if not the withdrawal of the drug.

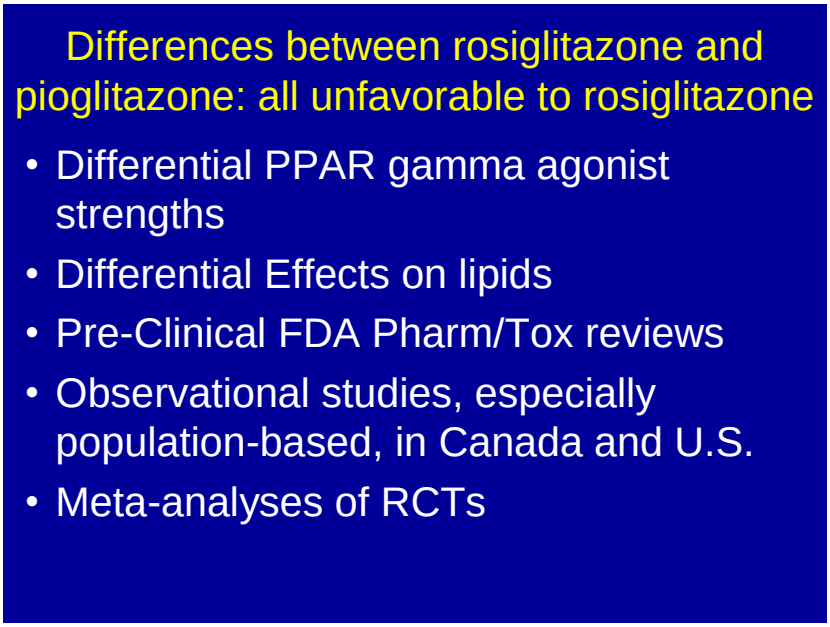
5. How should FDA factor in different kinds of safety evidence in considering different kinds of regulatory actions?

It is important here to stress one of the principal findings of the 2006 IOM study examining the drug safety system in the U.S: the need for "a systematic approach to risk–benefit assessments." This will only be meaningful if it is followed by patient-protective, appropriate regulatory decisions. Even in several instances in which liver toxicity was the reason for the withdrawal, FDA was extremely dilatory in its decision-making, resulting in many additional injuries and deaths to patients as a result of inappropriate prologation of the marketing life of these hepatotoxic drugs. The system within CDER for a "a systematic approach to risk–benefit assessments" is broken and needs to be significantly changed.

The following three very recent examples illustrate how a systematic approach to benefit risk assessments either was not accurately done by those in charge of CDER—again illustrating the conflict between OSE and OND/CDER leaders. They also illustrate how the U.S. regulatory conclustions differed, in scope or in timing, from those in Europe, where the precautionary principle seems to operate much more toward protecting the public health than here, where the precaution seems to be against taking definitive, appropriate regulatory actions.

Rosiglitazone (Avandia)

The following analysis of the problems with rosiglitazone was based application of the principles articulated in the IOM report to the FDA affecting the TIDE trial, presented last July. It is from my testimony at the 7/14/10 advisory committee hearing.



The following chronology was taken from information made public just before the FDA advisory committee meeting. We had asked FDA to ban the drug in July, 2007 and had filed a formal petition to accomplish this in October of 2008.

Conflict "Resolution" between OND and OSE

Date	OSE Finding	OND Response	Resolution
July 2007	Graham: withdraw rosiglitazone; Dal Pan: "balance of benefits and risks do not favor Rosiglitazone"	Do not withdraw:	Woodcock: More warnings but stays on the market; Ask GSK to do a study: TIDE (early '08)
October 2007	Dal Pan: "it is neither necessary nor appropriate to demand definitive statistical proof of a causal effect before taking regulatory action I support the overall conclusion that rosiglitazone be removed from the market."	Park: "the totality of data at present does not provide sufficient evidence to withdraw rosiglitazone from the market."	Woodcock (1/08): "Based on these findings, I do not believe that rosiglitzone should be withdrawn from the market. It needs to have a black box warning about the risk of MI in higher risk individuals, including those at risk by virtue of duration of their diabetes."

Source: Internal FDA memos made public for the first time in these hearing briefing documents

Conflict “Resolution” between OND and OSE

Date	OSE Finding	OND Response	Resolution
October 2009	Dal Pan: “The benefits of rosiglitazone do not outweigh its risks. I recommend granting the [Public]Citizen Petition’s request that FDA remove rosiglitazone from the market.”	Jenkins (11/09): leave on market; “I believe it is premature to reach a new Center decision on the cardiovascular safety of rosiglitazone and its marketing status before a full review of RECORD, and all other new data that have become available since the Center's 2007 decision, is completed and discussed at a public advisory committee meeting.”	Woodcock (12/09): Stays on market; reject petition for now and order more analyses of RECORD and have advisory committee meeting subsequently.

The EMA announced a suspension of Avandia marketing in late September. It stated that "the suspension will remain in place unless the marketing authorisation holder can provide convincing data to identify a group of patients in whom the benefits of the medicines outweigh their risks.”

On the contrary, the FDA decided to leave Avandia on the market with some restrictions of questionable practicality for new users of the drug that will not go into effect for a number of months. According to Dr. Woodcock, “We are not withdrawing the drug at this time because there is considerable uncertainty about this signal and whether or not it is valid.” In addition, hundreds of thousands of people currently using Avandia will continue to be exposed to the drug. The agency stated that “Current users of Avandia who are benefiting from the drug will be able to continue using the medication if they choose to do so.” During the first half of 2010, an average of more than 100,000 refill prescriptions a month were filled for Avandia in the U.S. Dr. Woodcock stated that there were, in late September, “600,000 people taking these products.”

Meridia (sibutramine)

Public Citizen, had petitioned the FDA in 2002 and again in late 2009 to ban sibutramine. Our original petition was prompted by findings from pre-approval RCTs of hypertension and increased pulse rate—both risk factors for heart attacks and strokes--along with cases of serious cardiac arrhythmias in people getting the drug. In addition, there were post-approval cases of heart attacks in young women, shortly after they had begun using sibutramine. Both the FDA medical officer reviewing the drug and, by a narrow vote, the FDA advisory committee voting before approval, were opposed to approval in 1996.

Because of these concerns same, the EMA, in 2004, ordered Abbott to do an RCT, known as SCOUT, to see if long-term use of sibutramine in obese patients would decrease cardiovascular risk. The overall findings from that study, showing significantly **increased** cardiovascular risk with sibutramine, were reviewed by both the FDA and the EMA last November with very different outcomes.

The EMA decided in January of this year to withdraw sibutramine, again stating that "benefits of sibutramine-containing medicines do not outweigh their risks, and therefore recommended that the marketing authorisations for sibutramine-containing medicines be suspended across the EU. The suspension will remain in place until the company can provide data that are sufficient to allow the identification of a group of patients for whom sibutramine's benefits clearly outweigh its risks."

The FDA, contrary to this, decided that the drug should stay on the market here, until there could be an advisory committee meeting and the FDA could examine the data from SCOUT.

The main findings from SCOUT can be seen in the following slide:

Major Findings from SCOUT Study

- 16 % increased risk of primary outcome in subutramine group
- 28% increased risk of non-fatal MI
- 36% increased risk of non-fatal stroke
- No group or subgroup with any evidence of clinical benefit from sibutramine

NEJM, September 2, 2010

Last month, the FDA belatedly convinced Abbott to withdraw marketing of the drug in this country, with an estimated 160,000 prescriptions for the drug filled in the U.S. between the EMA ban and the FDA ban.

Lessons learned from the sibutramine fiasco

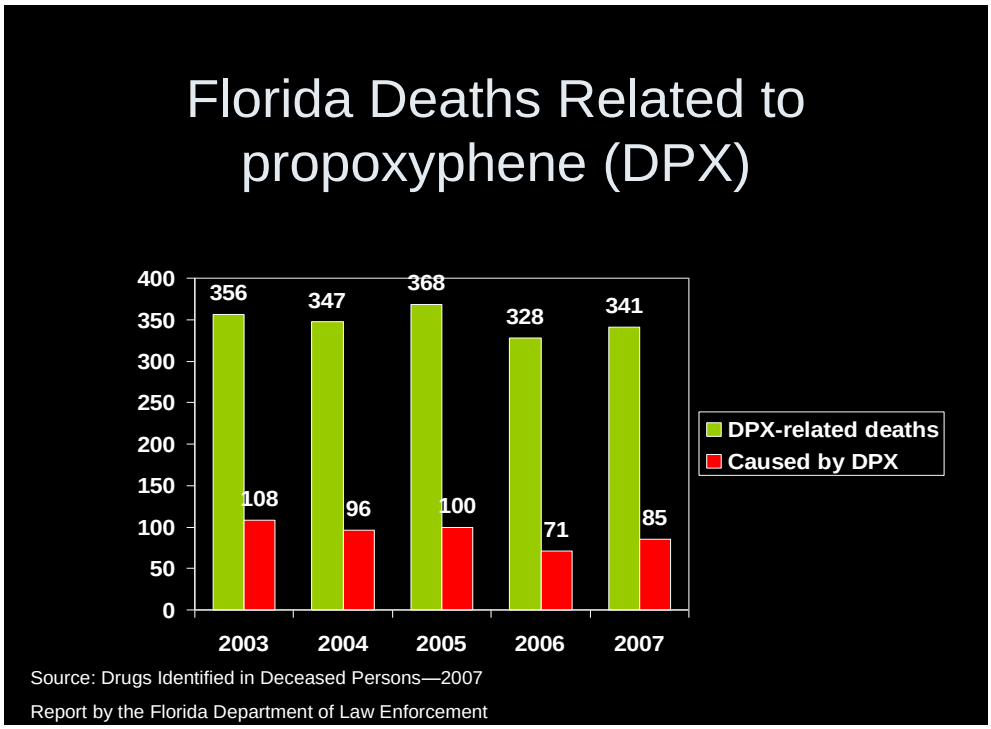
- The 1996 instincts/judgments of the FDA advisory committee and medical officer about increased cardiovascular risk of a drug that increases pulse rate, blood pressure and arrhythmias were correct.
- The FDA's zeal to replace the recently-banned Redux (the fen of fen-phen) with another weight-reducing drug was dangerous. From FDA Eric Colman's 2005 Annals historical review: "The void created by the withdrawal of dexfenfluramine in September 1997 was quickly filled with sibutramine [approved November 1997]."

Darvon/Darvocet (propoxyphene)

Public Citizen originally petitioned the FDA to ban this drug in 1978, based on evidence of its heart toxicity (impairing cardiac electrical conduction), especially with the metabolite norpropoxyphene that stayed in the body much longer than the parent drug. There were, by then, thousands of deaths in the U.S. attributed to the drug since it had come on the market in 1957. The FDA denied our petition. The UK announced, in 2005, it was phasing out the drug over a two-year period. The reasons stated by the UK for the ban were that the efficacy of this product "is poorly established and the risk of toxicity in overdose, both accidental and deliberate, is unacceptable." "Each year there are 300-400 fatalities following deliberate or accidental drug overdose involving co-proxamol [propoxyphene/acetaminophen] in England and Wales alone. Approximately one-fifth of these deaths [60-80] are considered to be accidental." They further said that "It has not been possible to identify any patient group in whom the risk-benefit [ratio] may be positive."

We again petitioned the FDA in 2006 to remove the drug from the U.S. market. In our February 2006 petition, we stated that "Adverse cardiovascular events are marked by prolongation of the QRS complex on an electrocardiogram (which can increase the risk for an abnormal cardiac rhythm) and include bundle branch block (interruption of cardiac conduction), bradycardia (slowed heartbeat), asystole (absence of contractions), diminished myocardial contractility (ability of the heart to contract), and hypotension."

The following information is from our January, 20009 presentation before FDA advisory committees concerning the safety of propoxyphene"



Details of 85 Florida DPX-Caused deaths: 2007

Type of Death	Accident	Suicide	Unspecified/ Natural
DPX as sole cause = 25	17	5	3
DPX+other drug(s) = 60	49	11	0
Total = 85	66	16	3

Source: Drugs Identified in Deceased Persons:2007 Data obtained from the Florida Department of Law Enforcement

222 Consecutive patients admitted to one Danish ICU with DPX intoxication

- 107 (48%) heart failure
- 12 (15%) asystole
- 21 (9%) bradycardia
- 91 (41%) abnormal ECG
  - 43(19%) QRS>120ms
  - 19 (8%) ventric. arrhyth.

Acta Anesthiol. Scand. 1984:28;661-665

In June, 2009, a proposed ban of propoxyphene was announced by the EMA stating that:

"In view of the complex context in which cases of fatal overdose occurred, and in view of the narrow therapeutic index and the potential for rapid death, the proposed restrictions to limit the use of dextropropoxyphene containing medicinal products such as narrowing the indication, reducing the pack sizes and/or introducing further safety warnings and contraindications are not considered sufficient to limit the risk of fatal overdose reported with dextropropoxyphene and appropriately ensure a safe and effective use of the product in the symptomatic treatment of pain.

"Therefore, the CHMP [the subgroup from which the EMA sought a consultation on this] concluded that the benefit-risk balance of dextropropoxyphene containing medicinal products is negative and recommended the withdrawal of the Marketing Authorisations for the medicinal products referred to in Annex I to be effected within the next 15 months in order to allow switching patients to safer alternatives in particular ,considering the extensive clinical use of dextropropoxyphene containing medicinal products and the wide patient exposure in some Member States."

Concerning efficacy, the conclusion was that "results from clinical trials do not provide evidence for the superior efficacy of dextropropoxyphene alone or in combination with paracetamol [acetaminophen] when compared with normal therapeutic doses of simple analgesics."

The following month, in July 2009, the FDA denied our 2006 petition to ban propoxyphene. Rather than looking at the accumulated evidence, the agency, in a manner similar to that of the propoxyphene manufacturer testifying during the January 2009 FDA hearing, proceeded to indiscriminately and inaccurately chop down certain trees and lose sight of the forest of adverse information that spelled out an extremely unfavorable benefit risk balance for the drug.

In August, we filed a petition for reconsideration with FDA Commissioner Hamburg. Our petition was supported by Dr. Donald Kennedy, who had been the FDA Commissioner in 1978 when our first petition was denied and by Dr. Richard Crout, who had been the Director of the FDA Bureau of Drugs, the predecessor to CDER. In the 15 months since this petition for reconsideration, we have had no response from the FDA.

During the four years and eight months since our 2006 petition to ban propoxyphene, approximately 90 million prescriptions have been filled in the United States for this drug which has the most unfavorably benefit risk ratio of any drug with which I am familiar.

In summary, these three examples demonstrate that one of the most important issues delineated in the October 27 2006 New England Journal of Medicine article by Psaty and Burke, summarizing the findings of the last IOM study on FDA Drug safety, has been frequently and dangerously violated since then: the need for "a systematic approach to risk–benefit assessments." Until the existing system is significantly altered to prevent further disasters such as these three and others, more health-threatening decisions will continue to be made by CDER.