Testimony of Sidney M. Wolfe, M.D., Public Citizen's Health Research Group

Before FDA Endocrinologic and Metabolic Drugs Advisory Committee Meeting on Cardiovascular Risk Assessment of Obesity Drugs

March 29, 2012

“A DANGEROUSLY LOW APPROVAL STANDARD HAS LED TO NEEDLESS DEATHS AND INJURIES FROM DIET DRUGS

Over 30 [now 44] years ago, in June 1968, FDA Medical Officer Dr. Robert O. Knox refused to approve the New Drug Application (NDA) for a diet drug. This disapproval touched off a dispute between the FDA and the drug’s manufacturer, A.H. Robbins, that eventually led to the drug’s approval and Dr. Knox’s transfer to another area within the Agency. His reason: obesity is a chronic disease and there is no evidence that these drugs affect the course of the disease over the long term. The drug Dr. Knox refused to approve was fenfluramine (Pondimin), a drug that ultimately became the “fen” portion of the notorious “fen/phen” combination, that was removed from the market on September 15, 1997.”

From Public Citizen FDA petition to ban sibutramine, March 19, 2002

Four obesity drugs withdrawn from the U.S. market in the past 15 years (1997-2012)

Obesity Drug	Year withdrawn	Cardiovascular adverse event(s)
fenfluramine/dexfen.	**1997**	**Pulmonary hypertension, Heart valve damage**
phenylpropanolamine (PPA)	**2001**	**Increased hemorrhagic strokes**
ephedra	**2004**	**Increased strokes, heart attacks**
sibutramine	**2010**	**Increased strokes, heart attacks**

Public Citizen Supports the New FDA Criteria for Obesity Drug Approvals

"any drug developed for obesity should not only be effective, but should demonstrate safety for long-term or chronic use in a large, diverse population."

Current FDA briefing package for this meeting, page 7.

Two Year Persistence Rates for Both Sibutramine and Orlistat were 2% Using Population-Based Data from a Canadian Province (British Columbia)

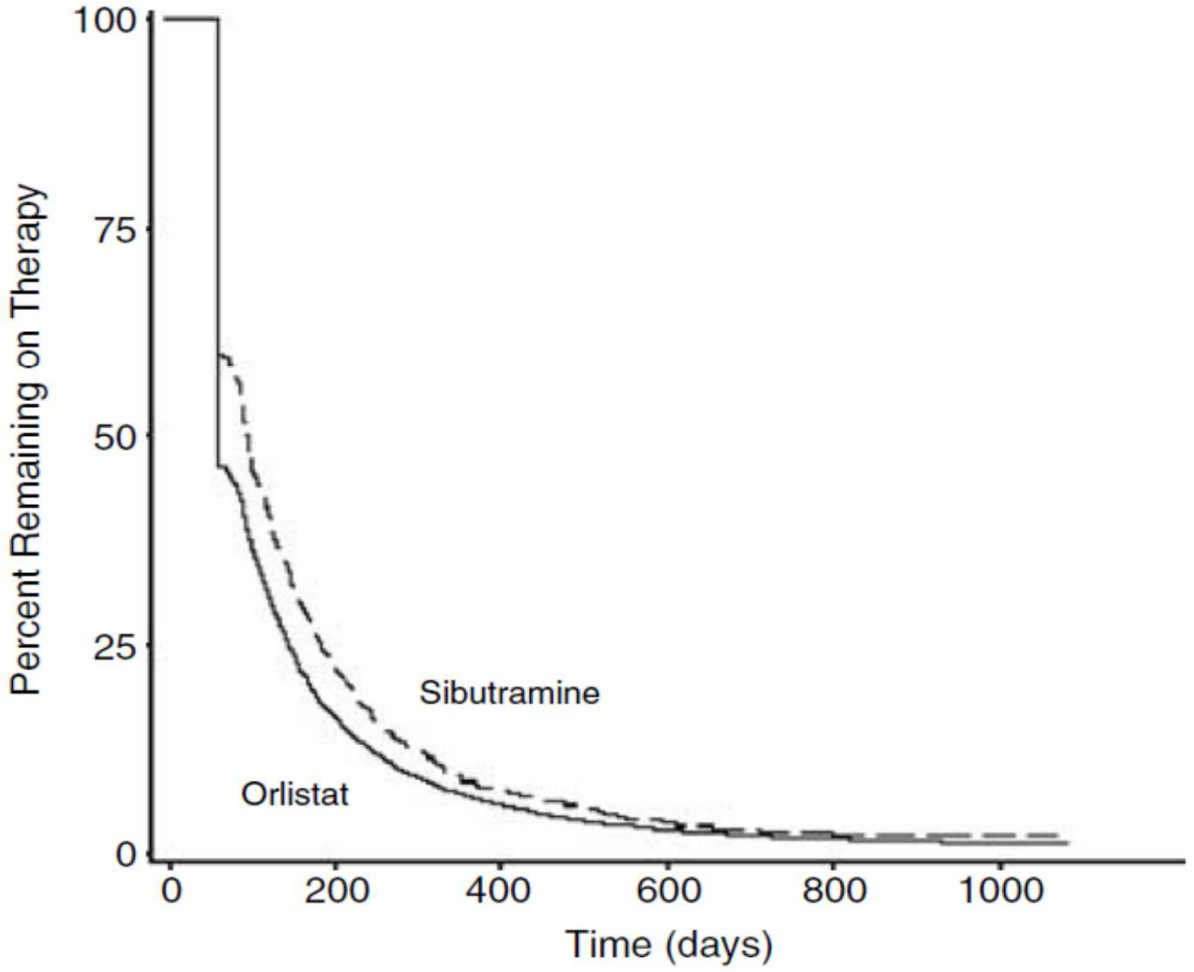

Figure 1 Kaplan–Meier llots demonstrating long-term persistence with orlistat and sibutramine

International Journal of Obesity (2007) 31, 1567–1570

- No possible benefit for most people using obesity drugs because of relatively short term use.
- But even during the relatively short time most people are on the drugs, significant harms are already occurring.
- Thus, for most of these people, there are risks without any chance of benefit.
- Long term use is really an artifact of trial design, as in SCOUT, but is necessary to establish the risk for longer term use.

Cumulative Number (%) of Subjects with Nonfatal Stroke, during the Randomization Phase

Nonfatal Stroke	Placebo N=4898 n (%)	Sibutramine N=4906 n (%)	Hazard Ratio	95% CI	p-value
6 months	11 (0.2)	26 (0.5)	2.39	1.18, 4.84	0.02
12 months	18 (0.4)	38 (0.8)	2.14	1.22, 3.74	0.01
24 months	43 (0.9)	71 (1.4)	1.67	1.14, 2.43	0.01
36 months	64 (1.3)	98 (2.0)	1.54	1.13, 2.11	0.01
48 months	85 (1.7)	122 (2.5)	1.45	1.10, 1.91	0.01
60 months	97 (2.0)	131 (2.7)	1.36	1.05, 1.77	0.02
Overall	98 (2.0)	132 (2.7)	1.36	1.05, 1.77	0.02

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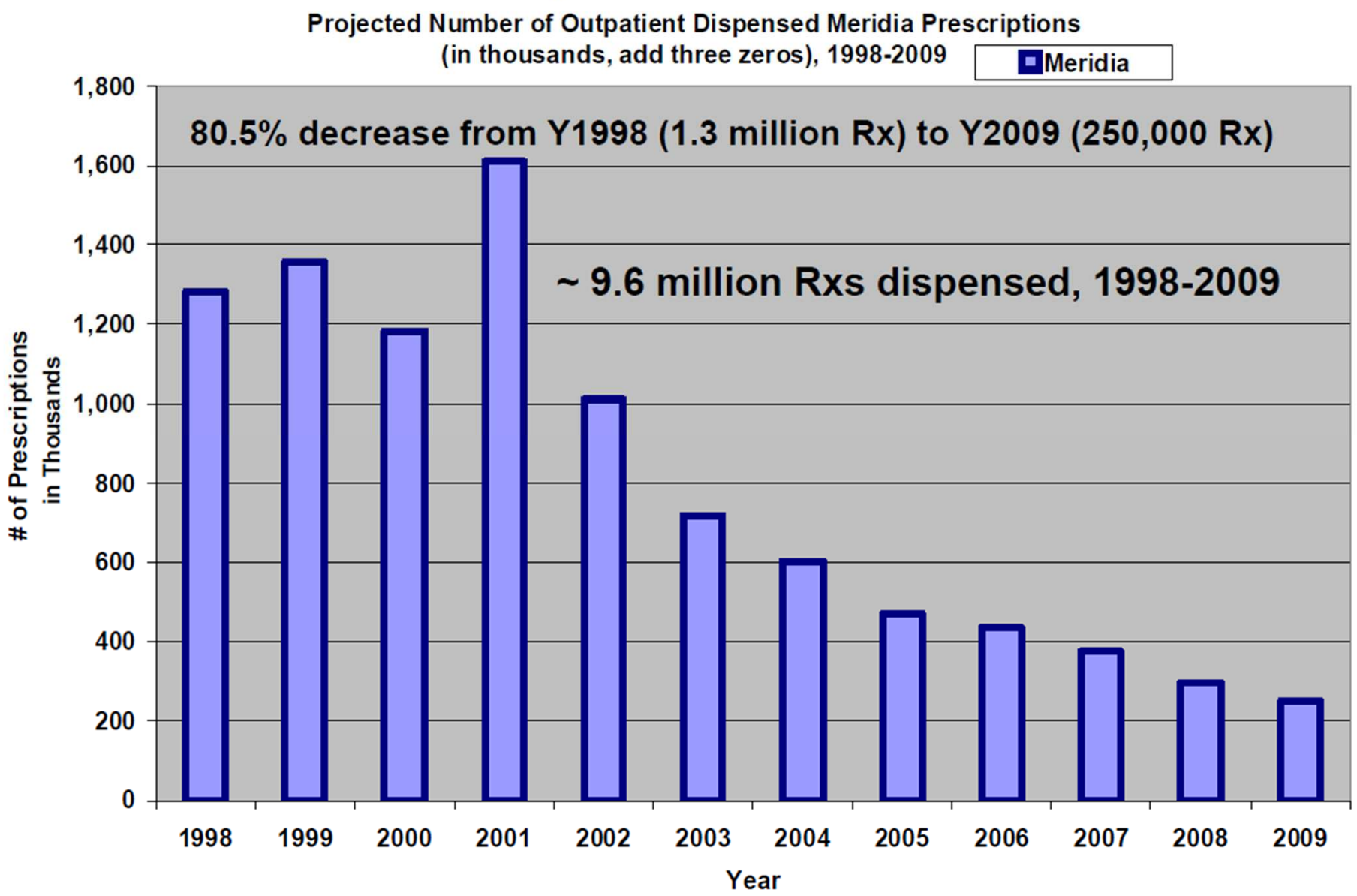
From 9/15/10 sibutramine advisory committee meeting, slide 24 (SCOUT results), FDA presentation by Dr. Falconer

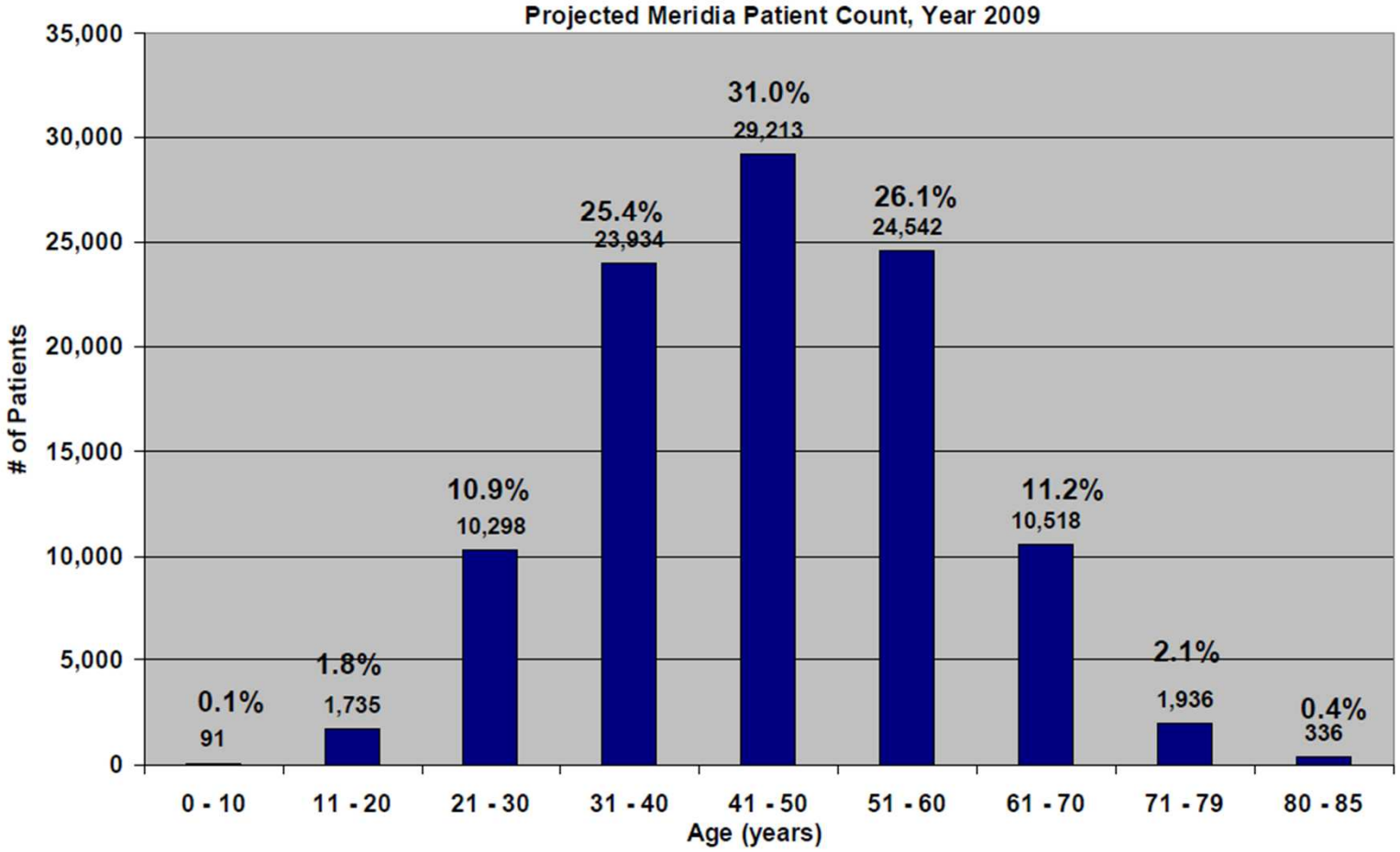
Outpatient Utilization



Source: SDI: Vector One®: National. File: VONA 2009-2201 sibutramine Trx1998-2009.xls

Outpatient Utilization

~ 94,000 patients in Year 2009; 83% female



**SDI, Total Patient Tracker. Data extracted 7-29-10 and 8-31-10.*

Files TPT 2009-2201 Meridia year 2009 4-15-10.xls, TPT 2009-2201 meridia age 10yr incr 2009 8-31-10.xls, TPT 2009-2201 Meridia year 2009 by gender 7-29-10.xls

Estimated People in US Exposed to Sibutramine

FDA estimate of 250,000 prescriptions filled in 2009, taken by 94,000 patients

If this ratio is constant, during its time on the market (through 2009):

9.6 million prescriptions were filled, taken by 3.6 million patients

"Not only is SCOUT a landmark study, it reminds us that there is no substitute for data from large, long-term controlled trials for making the most accurate assessment of a drug's risks and benefits. This fact will weigh heavily on the minds of FDA regulators as they, amid calls to reduce the size and scope of obesity drug registration trials, begin the process of updating the agency's *Guidance for the Clinical Evaluation of Weight-Control Drugs* (52)."

Dr. Eric Colman, Ann Intern Med. 2005;143:380-385.

Conclusions for Future Clinical Trials on Obesity Drugs

- There is little doubt that many thousands of people, of the 3.6 million U.S. patients using sibutramine, suffered heart attacks, strokes or other life-threatening adverse events caused by the drug.
- Had SCOUT been completed before approval instead of 12 years after, most of this damage would have been prevented.
- Given that no long-term randomized placebo-controlled study of any obesity drug has shown cardiovascular benefit, the benefits of doing future adequately powered trials before approval greatly outweigh the cardiovascular risks of waiting until there has been large-scale post-approval exposure.