

**Research-Based Consumer Advocacy:  
Data Analyses Facilitate Early Warnings  
to Patients,  
Withdrawals of Dangerous Drugs**

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# Situation Precipitating 3/21/71 Nader/Wolfe Letter to FDA Demanding Immediate Recall of Infected IV Fluids

150 reported cases of septicemia with 9 deaths from Abbott IV's--extremely unusual type of bacteria--infections stop when hospitals stop using Abbott IV's

Abbott/FDA/CDC response: no recall, use but: "At the first suspicion of ..septicemia or fever which might be associated with contaminated I.V fluid, all existent IV apparatus should be removed."

# Text of 3/21/71 Letter to FDA Commissioner Charles Edwards

Dear Dr. Edwards,

This is an urgent plea for immediate preventive action by the FDA to save lives and injuries. This action is within the knowledge and under the authority of your agency.... Despite evidence [of septicemia and deaths] the FDA has suggested continued use of these contaminated products with several handling precautions of questionable efficacy or practicality... The FDA is in possession of clear, unequivocal evidence and is not using its powers to get a documented serious hazard...off the market.....

# Criteria for Selecting Projects

- Severity of problem
- Number of people affected
- Availability/reliability of data
- Likelihood of change
- Likelihood of change by HRG action

# Methods for Research-Based Advocacy/Change

Research: Collect, analyze data, estimate risk, formulate petition to government agency, write report

Litigation: Against government if petition is not acted upon

Education, information: Teaching, Newsletters, Books, Medical Journal Articles, Print and Electronic Media; public “Right to Know” as regulation for OSHA, FDA, HHS

# Adverse Drug Reactions- Marketed Drugs

- 2,000,000 serious ADRs yearly
- 100,000 annual number of ADR-related deaths
- 4<sup>th</sup> -6<sup>th</sup>: ranking of serious ADRs as causes of death

**\$ 136,000,000,000 : annual cost**

"Which of these industries do you think are generally honest and trustworthy – so that you normally believe a statement by a company in that industry?" (Harris Poll 10/05, 1833 adults)

- Supermarkets 39%
- Banks 34%
- Pharmaceutical Companies 9%
- Tobacco companies 4%
- Oil companies 3%

# Varieties of Dangerous and Unacceptably Poor Drug/Device Industry/Gov't Practices

Failure to adequately/ ethically test products

Failure to report results to gov't agencies

Failure of government to regulate

Failure to accurately inform doctors  
and patients: false/misleading ads

## A Drug Company-sponsored Unethical Clinical Trial in Developing Countries

- Discovery Laboratories, Doylestown, PA
- Synthetic surfactant (Surfaxin)
- 4 surfactants on the market (1st in 1990)
- Associated with 34% relative reduction in neonatal mortality (Cochrane meta-analysis)  
“Without doubt the most thoroughly studied new therapy in neonatal care” (NEJM review)

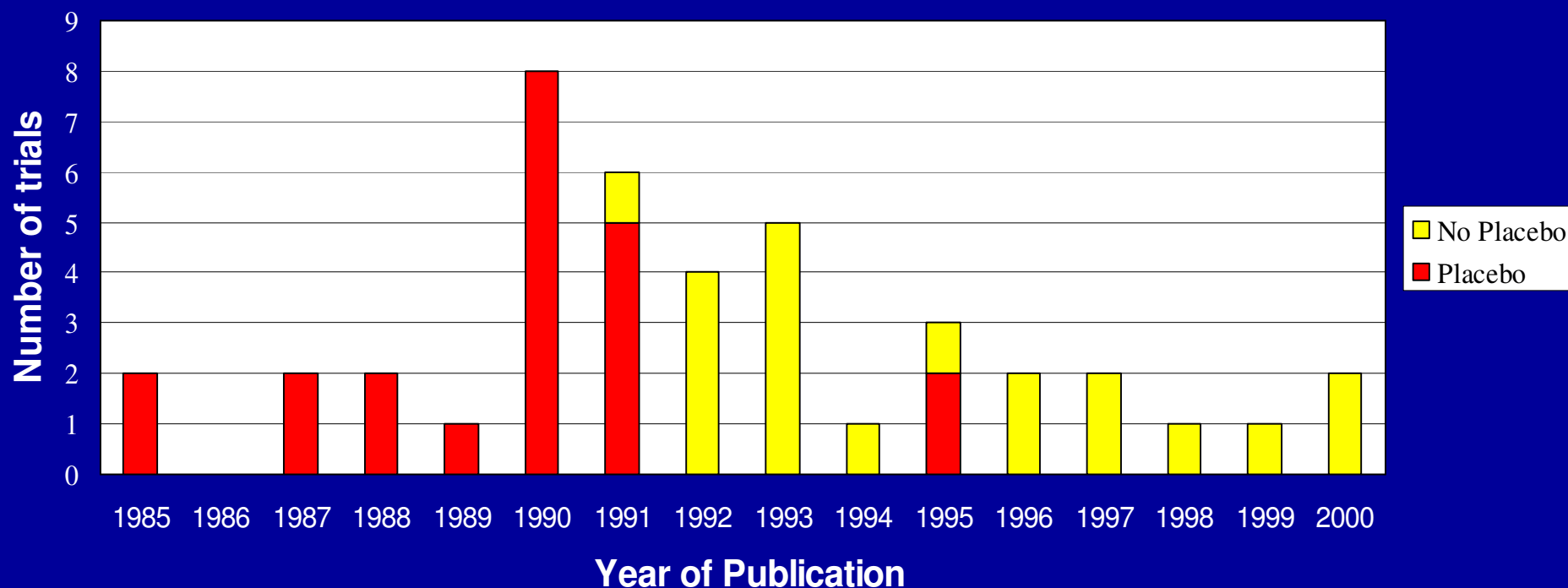
# A Drug Company-sponsored Unethical Clinical Trial in Developing Countries

- “Further placebo controlled trials of synthetic surfactant are no longer warranted.” (Cochrane)
- FDA: “Conduct of a placebo controlled surfactant trial for premature infants with RDS is considered unethical in the USA.”
- European trial: Surfaxin vs. approved surfactant

# A Drug Company-sponsored Unethical Clinical Trial in Developing Countries

- Title of internal FDA meeting: “Use of placebo-controls in life threatening diseases: is the developing world the answer?”
- Location: Mexico, Peru, Bolivia, Ecuador
- Design: Surfaxin vs. placebo (vs. approved surfactant)

# 42 Randomized Trials of Natural and Synthetic Surfactant in the Treatment of Neonatal Respiratory Distress Syndrome



# A Drug Company-sponsored Unethical Clinical Trial in Developing Countries

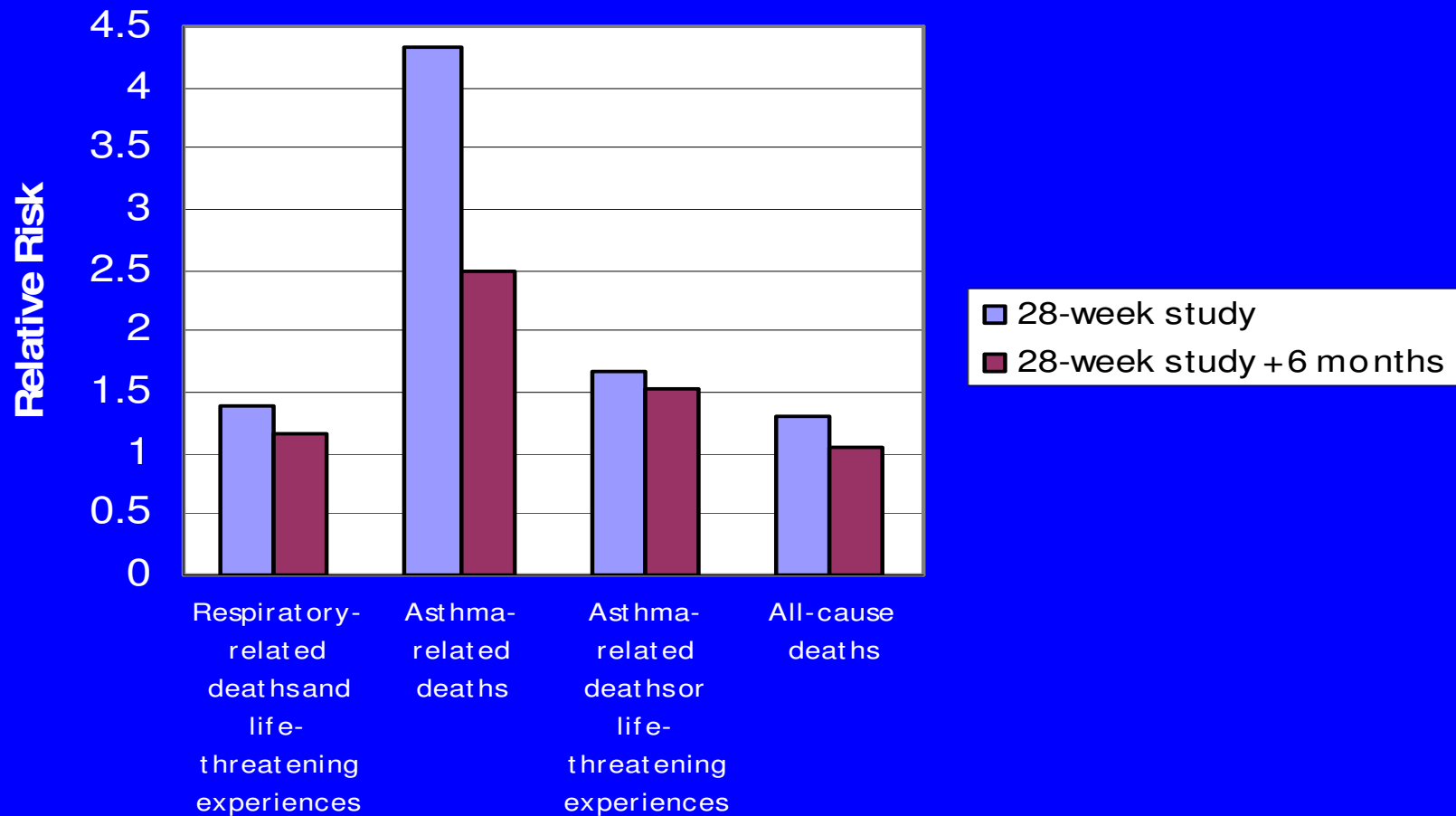
- February 2001: Public Citizen writes to HHS Secretary Tommy Thompson
- March 2001: Bolivian health ministry says the study is “totally prohibited” for legal, ethical and social reasons
- April 2001: Discovery announces study changed to compare to known effective surfactant

# Failure to Report Results to Government Agencies

## **Criminal Violations by Industry**

- Bjork-Shiley heart valve
- Selacryn: antihypertensive
- Oraflex: arthritis drug
- Merital: antidepressant

# Salmeterol Postmarketing Study (SMART)



Source: Lurie and Wolfe. Lancet 2005

# Failure of Government to Regulate

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- **Raw (unpasteurized) milk**
- **Aspirin and Reye's Syndrome**
- **Tampons and toxic shock**
- **Phenformin and lactic acidosis**
- **Posicor, Duract, Redux, Rezulin,**
- **Propulsid, Vioxx, Celebrex, many more**

## Acute Renal Failure and Suprofen

- **12/85: suprofen, a uricosuric NSAID first marketed**
- **9/25/86: HRG Petition to ban suprofen**
- **the first 51 cases of acute flank pain (acute renal failure) reported to FDA\* included 18 hospitalizations, 17 with hematuria, average creatinine of 3.03; mainly previously healthy young adults**
- **12/86: FDA advisory committee and FDA oppose ban; R. Temple: “a wide choice of [nsaid] agents should be available”**
- **5/15/87: suprofen withdrawn from the market**
- **\* Wolfe SM. New Eng J Med 1987; 316:1025**

## Rise and Fall of Rezulin: Part 1

- March, 1997: U.S. marketing begins
- Dec, 1997: drug withdrawn in UK after 130 cases of hepatotoxicity including six deaths
- July, 1998: Health Research Group petitions FDA to ban Rezulin after 560 cases of hepatotoxicity including 26 deaths

## Rise and Fall of Rezulin: Part 2

- March, 1999: FDA advisory committee meeting: FDA and HRG studies show < 5% compliance with Liver test recommendations; now 43 liver deaths reported
- early, 2000: Some FDA physicians now believe drug should be banned
- March, 2000: Rezulin is withdrawn in the US; by then, 63 liver deaths, seven transplants, more than 1000 cases of liver damage

# Trovan (trovafloxacin-antibiotic)

There was clear evidence of liver damage caused by Trovan before approval in December 1997. In one study in which the drug was used to treat prostatitis, almost 10% of the men given the drug developed evidence of liver toxicity. With dozens of other safer and equally or more effective drugs for infections, the removal of Trovan from the market would not have deprived doctors or patients of an indispensable drug. Instead of banning Trovan as was done everywhere else in the world, the FDA chose to “limit” its use in the United States to patients who were either hospitalized or in nursing homes. At the time of our 1999 petition in 1999 to ban the drug, there were eight cases of liver failure, including five deaths and three liver transplants. There are now a 56 cases of liver failure, including 29 deaths and nine people requiring liver transplants.

## **Baycol (cerivastatin-cholesterol lowering)**

Approximately one year before Baycol was removed from the market in August 2001, Bayer, using FDA data on other statins, found that Baycol had 20 times more reports of rhabdomyolysis (an often-fatal destruction of muscle) per million prescriptions than Lipitor. By the time Baycol was banned, there were 1,899 cases of rhabdomyolysis, a significant number having occurred between the time there was unequivocal evidence that FDA should have banned the drug and when it was actually banned a year later.

# Vioxx: Delayed Warnings

11/00 Published Vigor study shows 4-fold increased risk of MI with no other plausible explanation for this

2/01 HRG asks FDA for black box warning

3/01 HRG advises Worst Pills, Best Pills readers not to use Vioxx

12/04 second study confirms increased MI with Vioxx and drug is withdrawn

# Three Studies Demonstrating Suppression of FDA Decisions About Drug Safety

## **HRG Study, Fall 1998:**

Responses, from 53 FDA physicians, included 27 instances cited in which the FDA medical officer thought a drug too dangerous to be approved but approval occurred over their objection. Seventeen medical officers described the current standards of FDA review for safety and efficacy as "lower" or "much lower" compared to those in existence prior to 1995. Several medical officers said they had been instructed by their superiors to censor their reports or presentations.

# FDA Internal Study, 2001

Precipitated by high turnover rates among scientists and physicians in the agency, study showed that one-third of medical officers did not feel comfortable expressing differing scientific opinions, and a similar number felt that decisions adverse to a drug were stigmatized within the agency. A number of reviewers said that decisions should be based more on science and less on corporate wishes.

# Inspector General Study, 2003

Confirmed that decisions concerning drug safety and effectiveness were being overturned. Eighteen percent of surveyed FDA physicians and scientists felt pressure to recommend that drugs be approved for sale despite their reservations about the drug's safety, efficacy or quality. The report concluded:  
"Overall, these findings present a significant warning signal."

## Health Research Group Petitions to Ban Prescription Drugs: 1971-2006

- Number of petitions filed 28
- Examples: Abbott IV fluids, Ilosone, phenformin, Oraflex, Suprol, Feldene, Redux, Rezulin, Serzone, Crestor, Celebrex, Bextra
- # drugs withdrawn 18 (64%)
- # with use severely limited 5 (18%)
- # still widely used 5 (18%)

<b>Generic Name (Brand Name)</b>	<b>Date Withdrawn in US</b>	<b><i>Worst Pills, Best Pills</i> News Readers Warned DO NOT USE</b>
<b>Rofecoxib (VIOXX)</b>	<b>September 2004</b>	<b>April 2001</b>
<b>Nefazadone (SERZONE)*</b>	<b>May 2004</b>	<b>February 2002</b>
<b>Cerivastatin (BAYCOL)</b>	<b>August 2001</b>	<b>March 1998</b>
<b>Alosetron (LOTRONEX)**</b>	<b>November 2000</b>	<b>August 2000</b>
<b>Cisapride (PROPULSIDE)</b>	<b>March 2000</b>	<b>August 1998</b>
<b>Troglitazone (REZULIN)</b>	<b>March 2000</b>	<b>January 1998</b>
<b>Grepafloxacin (RAXAR)</b>	<b>October 1999</b>	<b>April 1998</b>
<b>Bromfenac (DURACT)</b>	<b>June 1998</b>	<b>December 1997</b>
<b>Dexfenfluramine (REDUX)</b>	<b>September 1997</b>	<b>July 1996</b>

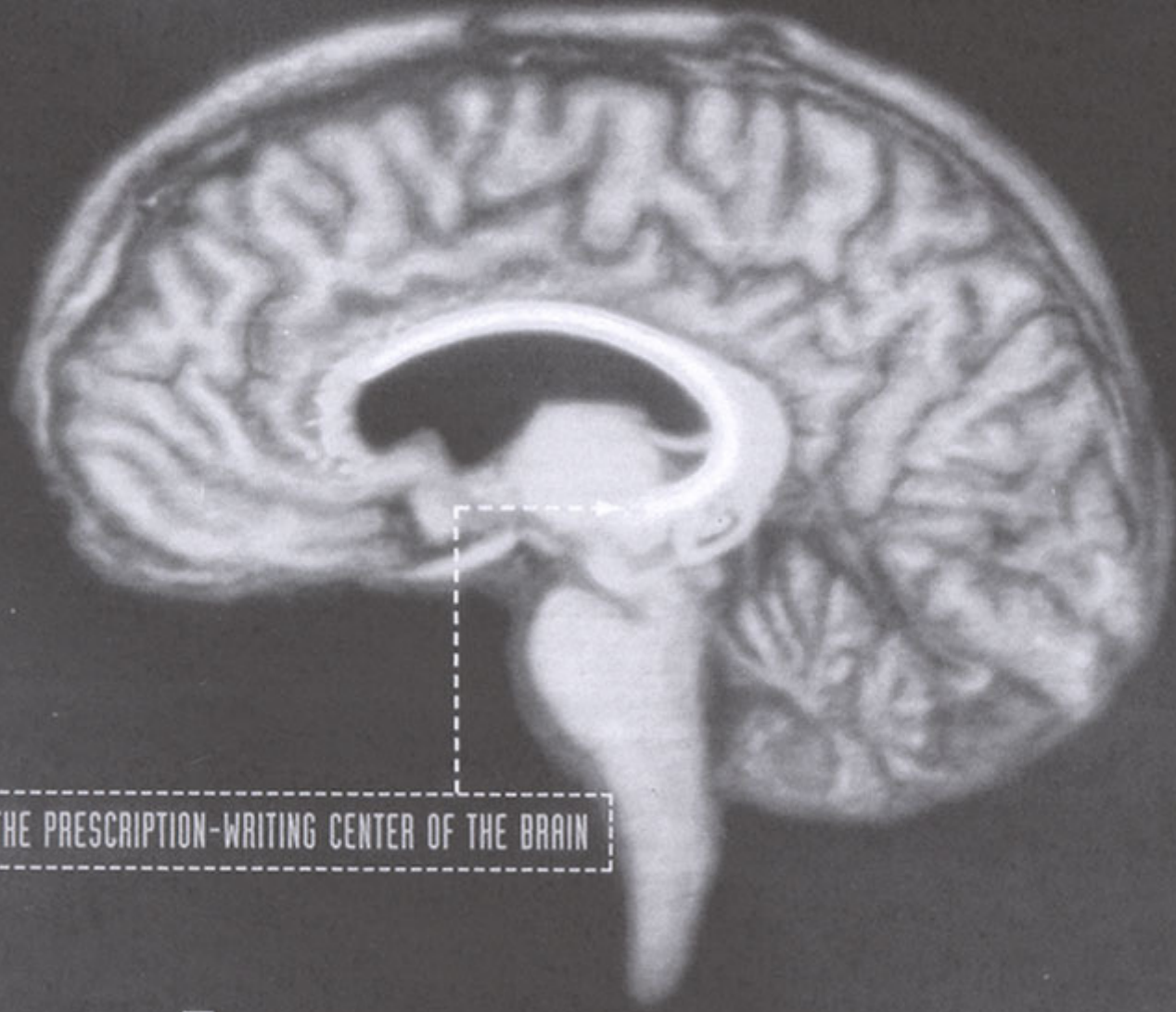
Failure to accurately inform doctors  
and patients: false/misleading ads  
and doctor-bribing

# Advertising Defined

“the science of arresting the human intelligence long enough to get money from it”

Definition of advertising by Canadian economist, Stephen Leacock. *The Garden of Folly*, 1924

# STRAIGHT TO THE HIPPOCAMPUS



THE PRESCRIPTION-WRITING CENTER OF THE BRAIN

**T**he hippocampus is the area of the brain that converts new information and new ideas into permanent memory. It processes information by connecting new concepts with the parts of the brain where gut instincts are formed. areas

Ad from ad  
agency to  
marketing  
departments  
of drug  
companies

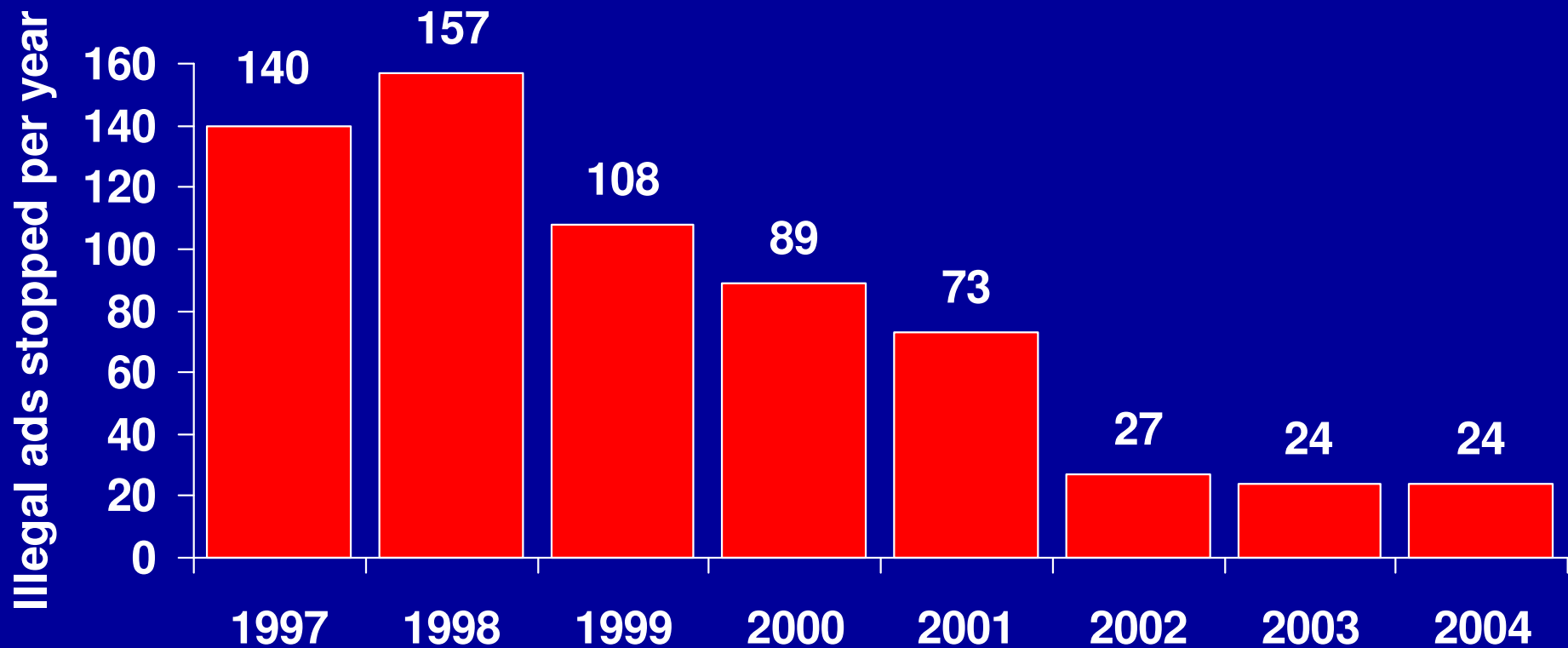
# Straight to the Hippocampus: What Drug Ad Marketeers Promise Drug Companies They Will Deliver

the hippocampus “processes information by connecting new concepts with the parts of the brain where gut instincts are formed, areas that influence emotional behavior and form memories..... communications are focused on making the [doctor’s] hippocampus respond positively to your product [by demonstrating] how your product is superior and unique”

Wolfe S. Lancet 1996;348:632.

# FDA Drug Advertising Enforcement: 1997-2004

FDA Warning and Notice of Violation Letters to Drug Companies



[www.WorstPills.org](http://www.WorstPills.org)

# **URL to Allow People in Developing Countries Free Access to Worstpills.org**

[http://www.worstpills.org/http\\_IPCountryCheck.cfm](http://www.worstpills.org/http_IPCountryCheck.cfm)

**Please e-mail this URL to your colleagues in developing countries**

# The FDA Web Site

[www.fda.gov](http://www.fda.gov)

- Enormous
- User unfriendly
  - Better than it used to be
- Filled with regulatory jargon
- Some agency documents are available under the Freedom of Information Act (FOIA)

Click on drugs (left bar)

# FDA Review Documents

- Agency's review of data submitted by manufacturers for new drug approval
  - Medical officer review
  - Pharmacology/toxicology
  - Biopharmaceutics/pharmacokinetics
  - Statistics
  - chemistry
- May contain unpublished clinical trials
- Some as large as 300 or 400 pages

# FDA Review Documents

- These documents provide the most complete picture of a drug's safety at the time of approval (not web-available until varying times after approval)

Date of approval can be found at [Drugs@FDA](#) on drugs page

# FDA Review Documents

- Click on Drugs@FDA on the drugs page
- Enter brand or generic name in search box
  - Follow links to Approval History and Related Documents
  - Click of the Review link for the documents
    - Review documents for new uses for old drugs are also available (supplementals)
- Covers drugs approved back to 1998
- For drugs approved before 1998

<http://www.fda.gov/cder/foi/nda/index97.htm>

# Advisory Committee Briefing Documents

- Preliminary FDA efficacy and safety reviews of new drugs before they are approved. (web-available at least 24 hours before meeting)
  - Only about 30% of new drugs are discussed at open public advisory committee meetings.
- These documents must be made available to the public before advisory committee meetings.
  - Result of a Public Citizen lawsuit

# Advisory Committee Briefing Documents

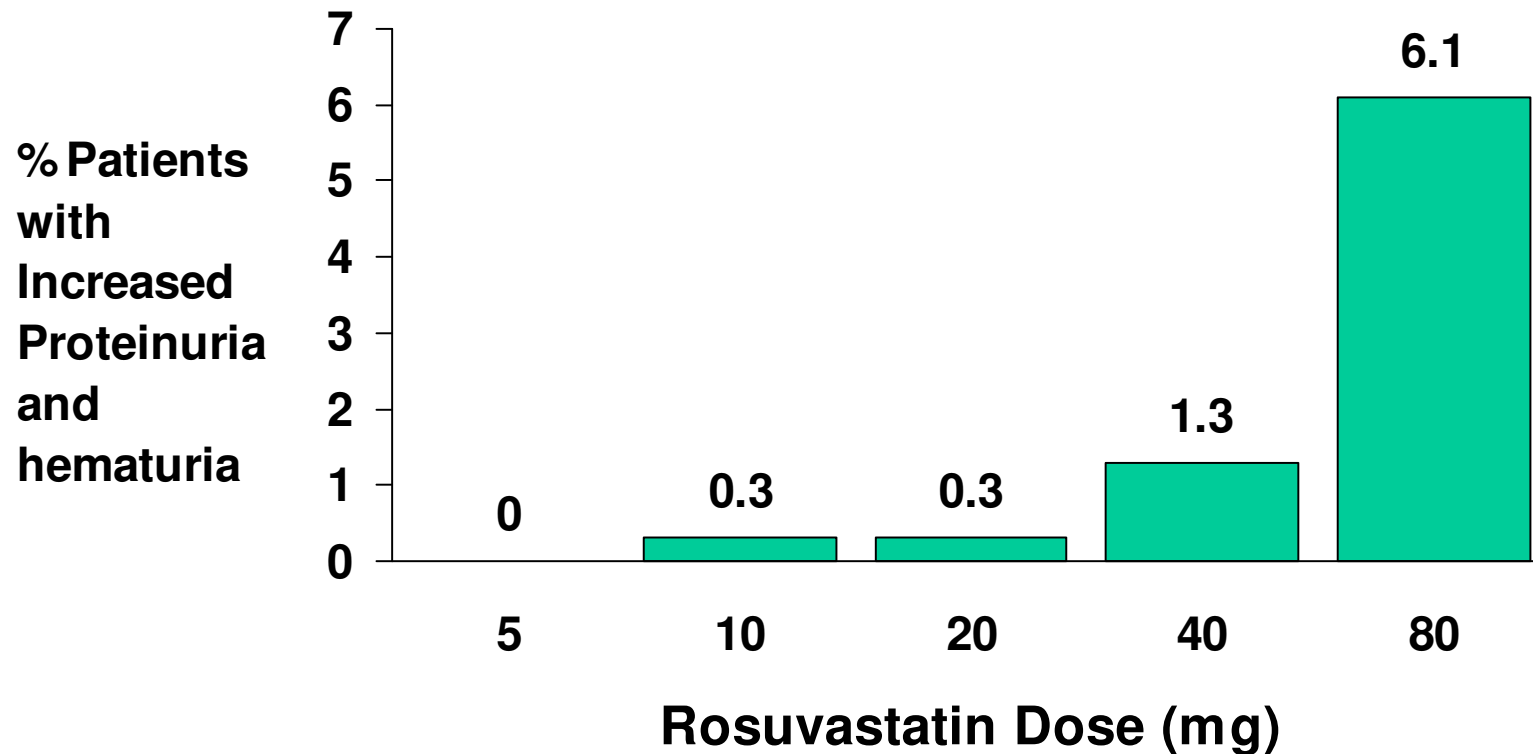
- Must know the name of the advisory committee and the date of the meeting.
  - Upcoming Meetings
    - <http://www.fda.gov/opacom/hpmeetings.html>
- Materials posted on the Dockets Web page
  - <http://www.fda.gov/ohrms/dockets/ac/acmenu.htm>
  - Organized by year and center

# Advisory Committee Briefing Documents

- Dockets site also gives access to:
  - Meeting minutes
  - Slide presentations
  - Meeting transcripts
  - Conflicts of interest

Data Made Available by the FDA  
Prior to July, 2003 Advisory  
Committee Meeting to Consider the  
Approval of Rosuvastatin

# Increased Proteinuria and Hematuria with Increased Rosuvastatin Dose



Data from Table 15,  
FDA presentation

## FDA Medical Officer Statement before Rosuvastatin Approval

“These three cases of renal insufficiency of unknown etiology are of concern because they present with a clinical pattern, which is similar to the renal disease seen with rosuvastatin in these clinical trials. There is mild proteinuria associated with hematuria and the suggestion of tubular inflammation or necrosis... if they [proteinuria and hematuria] are the signals for the potential progression to renal failure in a small number of patients, this may represent an unacceptable risk since currently approved statins do not have similar renal effects.”

# Supplement to Petition to Ban Crestor: October 29, 2004

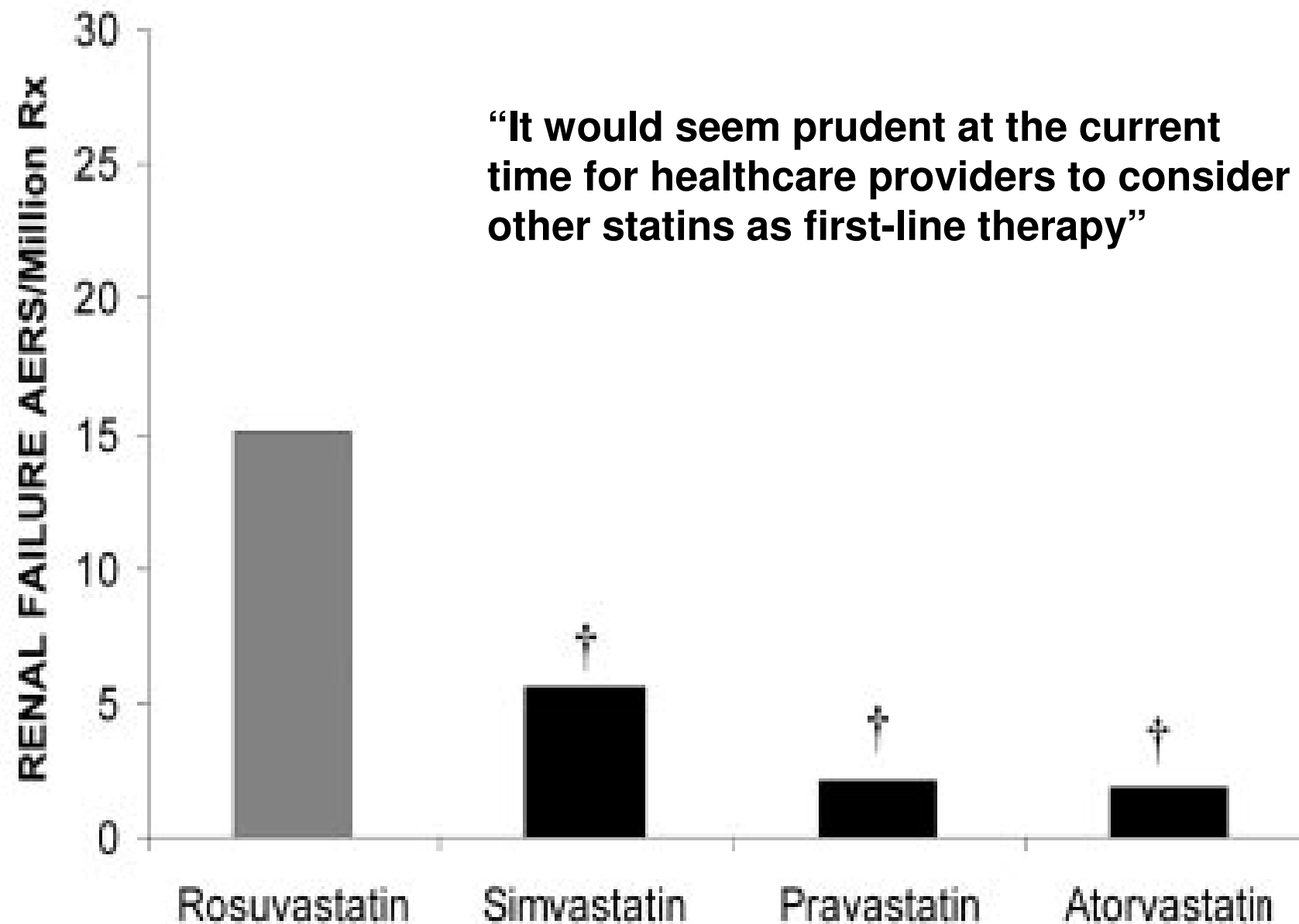
- 29 U.S. cases of acute renal failure or insufficiency (without rhabdomyolysis): a rate of 75 times higher per million prescriptions than all other statins
- 65 U.S. cases of rhabdomyolysis, a rate per million prescriptions higher than all other statins except for the banned Baycol

# Supplement to Crestor Petition Concerning Rhabdomyolysis

Comparative Rates of Rhabdomyolysis Reports to FDA  
10/1/03- 9/30/04

	# cases	Rx's	Cases per Million Rx	x Crestor is higher
Crestor	68	5.2	13.1	----
Zocor	139	29.8	4.7	2.8
Mevacor	16	8.0	2.0	6.6
Lipitor	87	66.6	1.3	10.1
Lescol	2	2.1	0.95	13.8
Pravachol	9	15	0.60	21.8
All statins but Crestor	253	121.5	2.1	6.2

**G**



[Alsheikh-Ali AA](#), [Ambrose MS](#), [Kuvin JT](#), [Karas RH](#).  
Circulation. 2005 Jun 14;111(23):3051-7. (all p<.001)

# Adverse Drug Reactions

- MedWatch
  - <http://www.fda.gov/medwatch/safety.htm>
  - Drug safety information and adverse event reporting.
  - Safety alerts for drugs, biologics, devices, and dietary supplements.
  - Safety labeling changes.
  - Can join list serve to receive safety alerts by e-mail

# FDA Approved Professional Product Labels

- Drugs@FDA
  - <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/>
- Collaboration between FDA and the National Library of Medicine

# Clinical Trials in Children

- Best Pharmaceuticals for Children Act of 2002
- Gave incentives to companies to conduct clinical trials in children for drugs already approved in adults.
  - Company receives 6 months of exclusivity regardless of study outcome.
- Contains summaries of unpublished clinical trials.

# Clinical Trials in Children

- Summaries of Medical and Clinical Pharmacology Reviews of Pediatric Studies

- <http://www.fda.gov/cder/pediatric/Summaryreview.htm>

[www.WorstPills.org](http://www.WorstPills.org)