



# Vioxx Science and Clinical Studies from a Legal Perspective

Vioxx Litigation Conference - Philadelphia



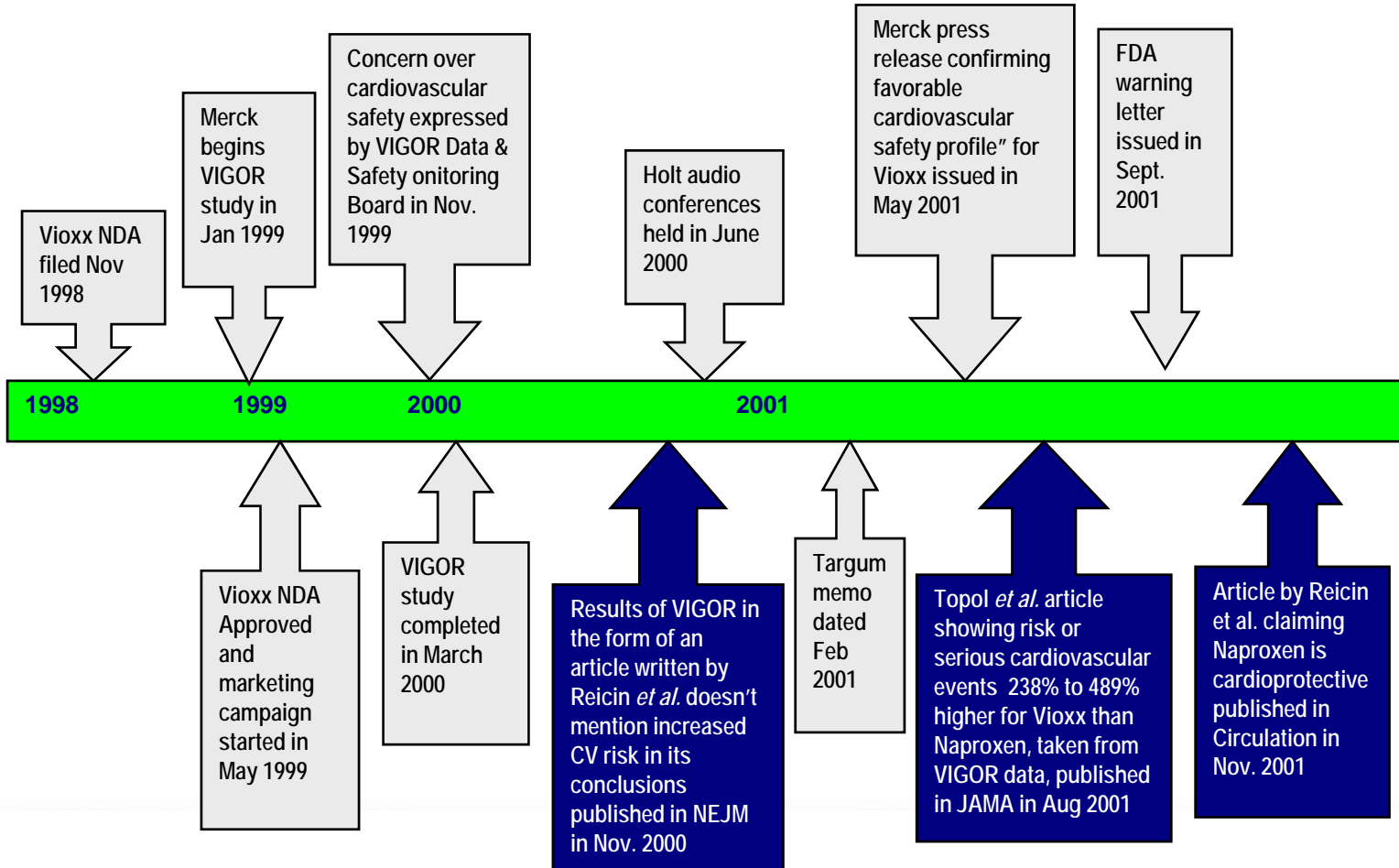
Barry Hill

Anapol, Schwartz, Weiss, Cohan, Feldman & Smalley, P.C.  
Wheeling, West Virginia  
[www.anapolschwartz.com](http://www.anapolschwartz.com)

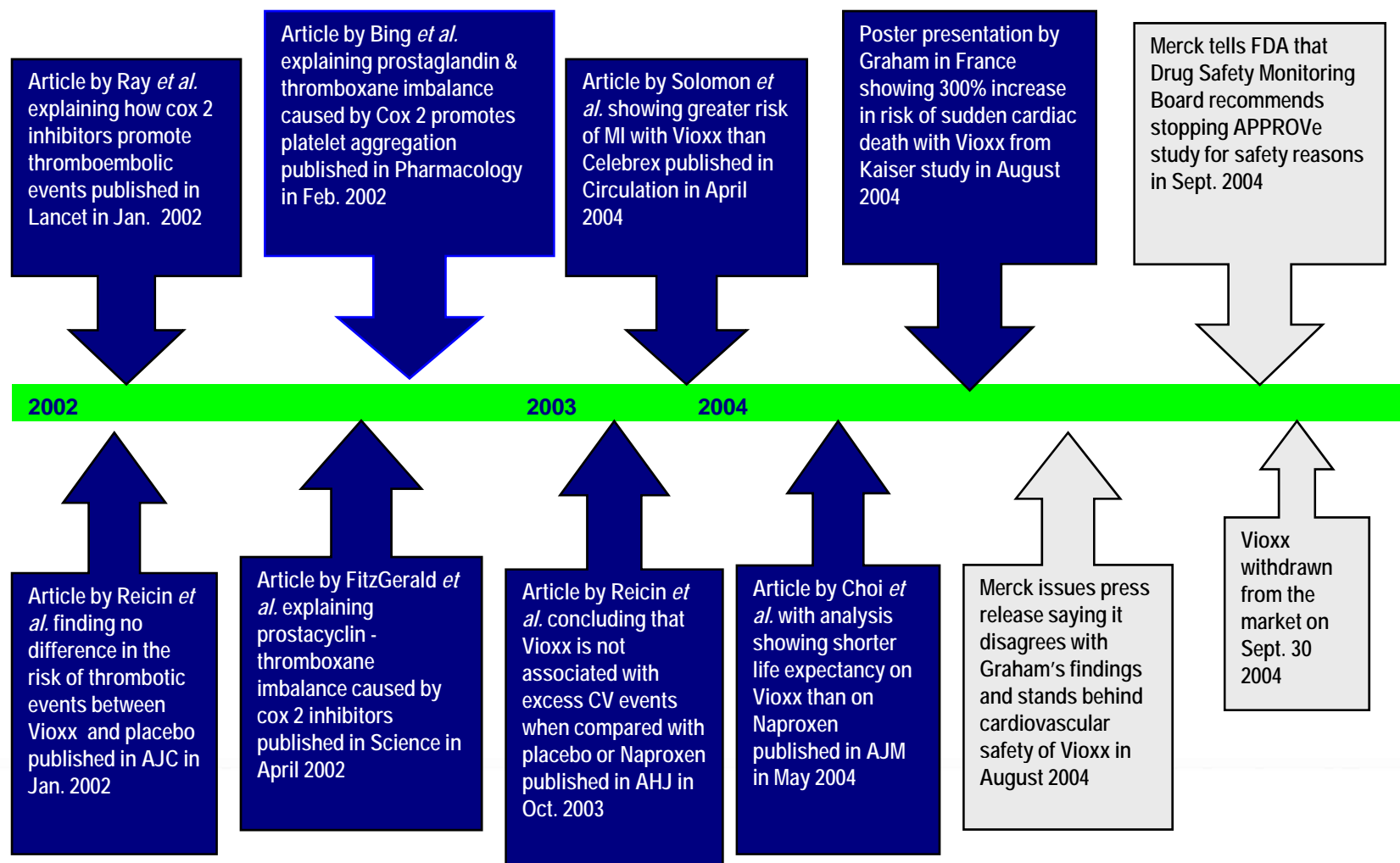


## Vioxx Medical Literature Timeline

2000 & 2001



## Vioxx Medical Literature Timeline- 2002 through withdrawal



# Broad guidelines for medical literature and studies as evidence in drug cases

- **Studies and literature published after the harm is done to a person usually is not relevant to the issue of the manufacturer's fault.**
- **Studies and literature published after the harm is done to a person can be relevant to general or specific causation.**

# Maintain reasonable skepticism when evaluating the validity of published drug studies and related published literature.

**“Medical journals are an extension of the marketing arm of drug companies.”**

**Richard Smith**

**Chief executive, United Health Europe**

**Formerly editor BMJ**

# “Journals have devolved into information laundering operations for the pharmaceutical industry”

**Richard Horton, editor, Lancet  
New York Review of Books, March 11, 2004**

**“ [The pharmaceutical industry] has moved very far from its original high purpose of discovering and producing useful new drugs. Now primarily a marketing machine to sell drugs of dubious benefit, this industry uses its wealth and power to co-opt every institution that might stand in its way, including the U.S. Congress, the Food and Drug Administration, academic medical centers, and the medical profession itself.”**

**Marcia Angell,  
former editor, NEJM**

# Journal deals available to advertisers

- Favourable editorial mention in exchange for an ad
- Will publish a particular paper if advertiser places an ad
- Ad alongside favorable article
- Tell advertisers what will be in the journal
- Product news
- Keep out unfavourable studies
- Ads on editorial pages
- False covers
- Reprints

# **Trials published in journals**

- **Credibility of the journal is attached**
- **Worldwide distribution**
- **Possible broad media coverage**
- **Much more valuable to companies than advertisements**

## Two thirds of trials in major journals are funded by the drug industry.

<i>Journal</i>	<i>Total trials</i>	<i>% drug trials</i>
<i>AIM</i>	<i>20</i>	<i>65</i>
<i>JAMA</i>	<i>47</i>	<i>64</i>
<i>Lancet</i>	<i>82</i>	<i>67</i>
<i>NEJM</i>	<i>83</i>	<i>74</i>
<i>BMJ</i>	<i>48</i>	<i>31</i>

Egger, M *et al.*, BMJ 2001; 323: 773

# Companies get the results they want

**A review of 56 published studies of non-steroidal anti-inflammatory drugs showed that not one was unfavourable to the sponsoring company.**

**All showed the sponsoring manufacturer's drug to be as good as, or better than, the that to which it was in terms of efficacy and/or toxicity.**

**Rochon PA, Gurwitz JH, Simms RW, Fortin PR, Felson DT, Minaker KL, *et al.*,  
Study of manufacturer supported trials of non-steroidal anti-inflammatory drugs  
in the treatment of arthritis. Arch Intern Med 1994;154: 157-63.**

# Some of the ways to design a study to yield the desired results

- **Trial against a drug known to be inferior.**
- **Trial against low dose of competitor to yield efficacy advantage.**
- **Trial against high dose of competitor to yield toxicity advantage.**
- **Trial against a superior competitor that is too small to show a difference to show equivalence.**
- **Use multiple endpoints and then, after the study is done, pick the ones that give positive results.**
- **When the study as a whole does not show positive results, do subgroup analyses and select positive results where found.**

# Publishing strategies

- **Suppress negative studies by not making them available for publication.**
- **Publish positive studies more than once by using supplements or other means.**
- **Conduct a multi-center trial and publish the results of the individual centers, as if they were separate trials, selectively if beneficial.**
- **Publish different outcome measures at different times to give the impression that results published later are from a new or different study.**
- **Publish different follow periods at different times, e.g., three-month results, one-year results, two-year results, to give the impression that more than one study was done.**
- **Publish positive results in major journals and negative or neutral results in minor journals.**
- **Combine the results of multiple trials in ways that are more favorable than any individual trial on its own.**

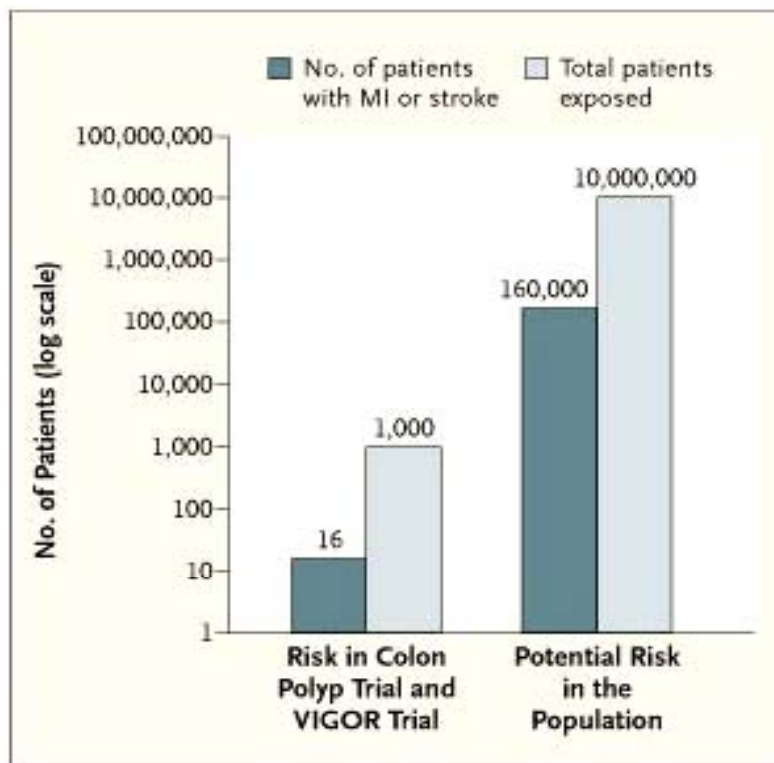
# Risk of myocardial infarction or stroke associated with Vioxx use.

*Failing the Public Health — Rofecoxib, Merck, and the FDA*

**Eric J. Topol, M.D.**

**NEJM**

**October 21, 2004**



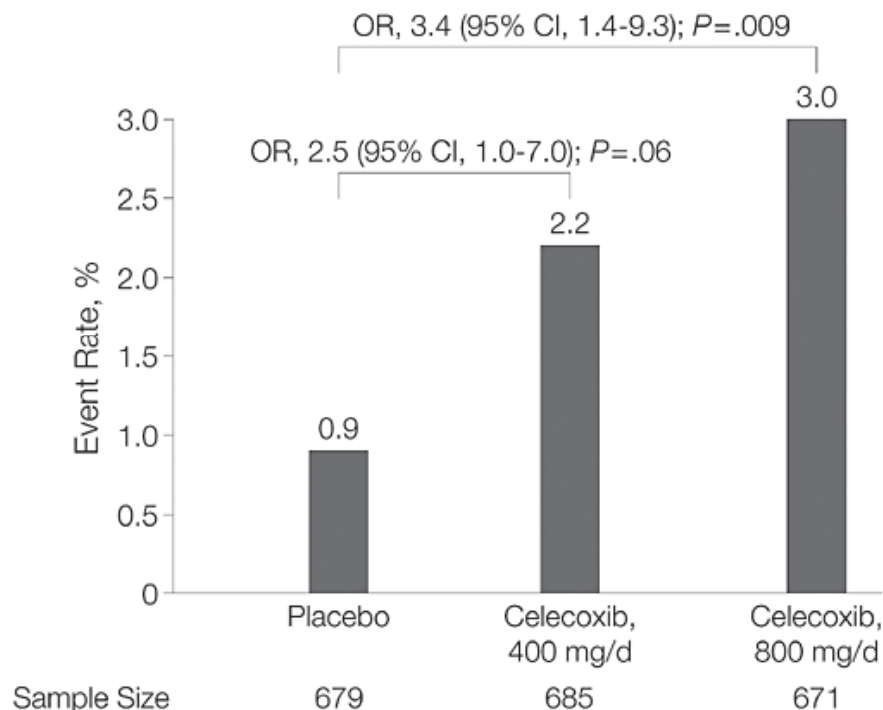
## Event rates of cardiovascular death, myocardial infarction, and stroke in the Adenoma Prevention with Celecoxib (APC) Trial

### *Arthritis Medicines and Cardiovascular Events—"House of Coxibs"*

**Eric J. Topol, M.D.**

**JAMA.**

**December 28, 2004**



## Meta analysis of 18 randomized controlled trials and 11 observational studies.

- **By the end of 2000 the relative risk in the randomized controlled trials was 2.30.**
- **One year later it was 2.24.**
- **There was little evidence that the relative risk differed depending on the control group (placebo, non-naproxen NSAID, or naproxen) or on the duration of the trial.**
- **In observational studies, the cardioprotective effect of naproxen was small and could not have explained the findings of the VIGOR trial.**
- **Rofecoxib should have been withdrawn several years earlier.**
- **The reasons why manufacturer ... did not continuously monitor and summarize the accumulating evidence need to be clarified.**

Risk of cardiovascular events and rofecoxib: cumulative meta-analysis.  
*Nartney et al., Lancet, Dec. 4, 2004*