

# Change Can Happen: New Trends in Clinical Trials in the U.S.

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SEARCH

**hot issues**

- ∴ **Public Citizen statement on Ralph Nader's campaign**
- ∴ Oct. 29 - New report links offshoring of U.S. jobs to Bush policies and campaign cash
- ∴ Oct. 29 - Rate of kidney damage in Crestor patients is 75 times higher than in patients taking other cholesterol drugs
- ∴ Oct. 4 - U.S. businesses file four times more lawsuits than private citizens



**featured publications**

- ∴ **Courting Change: The Story of the Public Citizen Litigation Group**
- ∴ **The Medicare Drug War: Drug Companies and HMOs Led an Army of Nearly 1,000 Lobbyists to Promote Misguided Legislation**
- ∴ **Whose Trade Organization? A Comprehensive Guide To the WTO - a new book by Lori Wallach and Patrick Woodall**

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**president's view**

Joan Claybrook Addresses Presidential Campaign

**White House Sides With Corporate Cronies**








Despite the tidal wave of corporate scandals that drained trillions of dollars from worker retirement accounts, shareholders and the economy, the Bush administration joined forces with the country's wealthiest CEOs to gut a proposed Securities and Exchange Commission regulation that would give shareholders more power to influence the behavior of corporate boards. Employees of the 205 corporations that opposed the measure contributed \$55.5 million to Bush's campaigns, his inauguration and the Republican National Committee since the 2000 election cycle.

To read Public Citizen's report, [click here](#).



To read the press release, [click here](#).

**Highlighted Campaigns**

**public citizen divisions**

-  Auto Safety
-  Congress Watch
-  The Critical Mass Energy and Environment Program
-  Global Trade Watch
-  The Health Research Group
-  The Litigation Group
-  BUYERS UP! Metro DC Home Heating Service

**state offices**

-  California Office
-  Texas Office

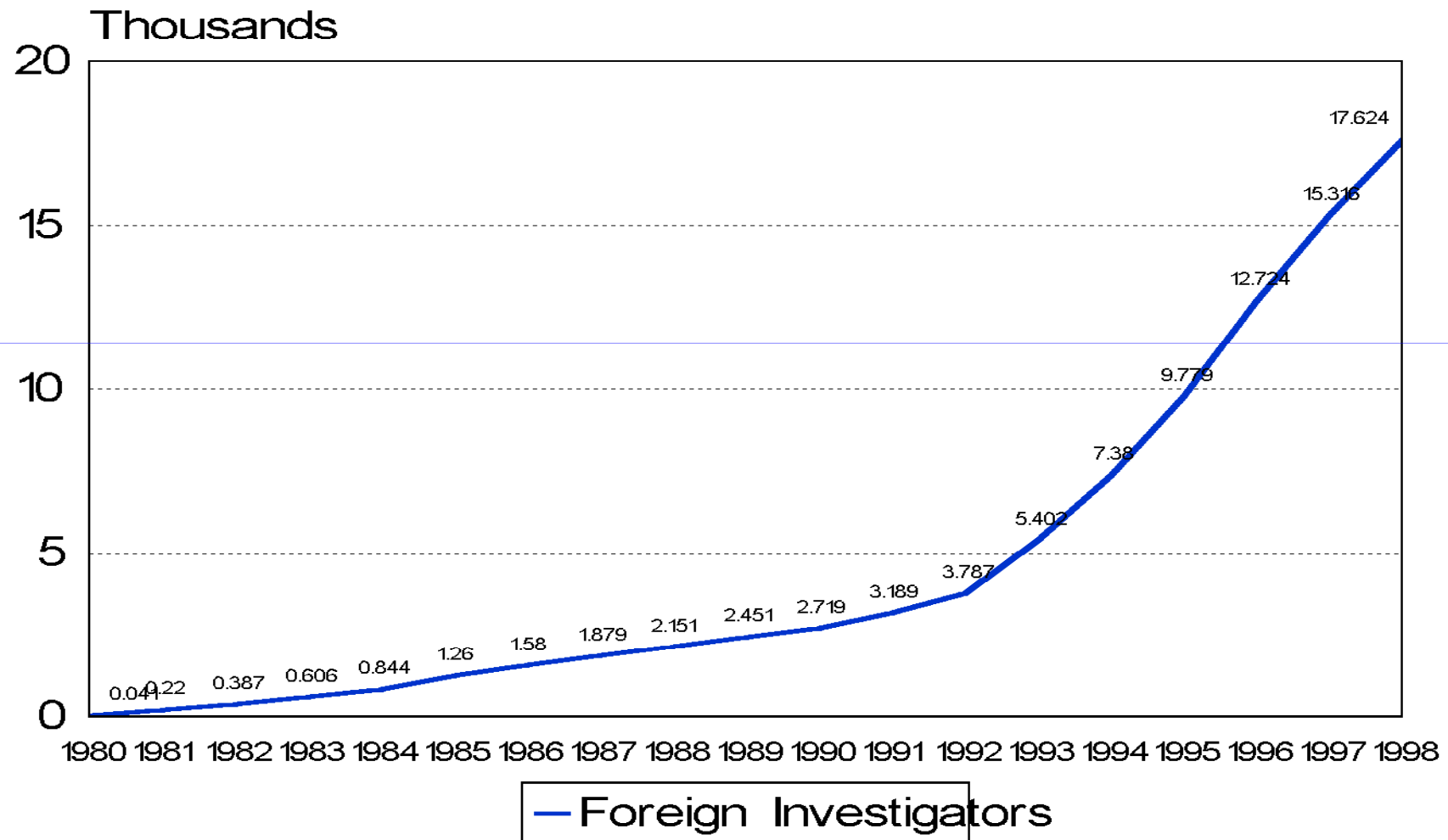
# Outline

- Ethics of developing country trials
- Access to data at the FDA
- Phase I GMPs
- Conflict of interest in FDA advisory committees
- Clinical trials registries
- Cough and cold
- Medical devices
  - VNS
  - Collagen scaffold
- Direct-to-consumer advertising
- Off-label promotion
- Changes Being Effected (CBE) supplements

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# Cumulative Number of Foreign FDA-Registered Clinical Investigators



Data supplied by the FDA to the HHS Office of Inspector General

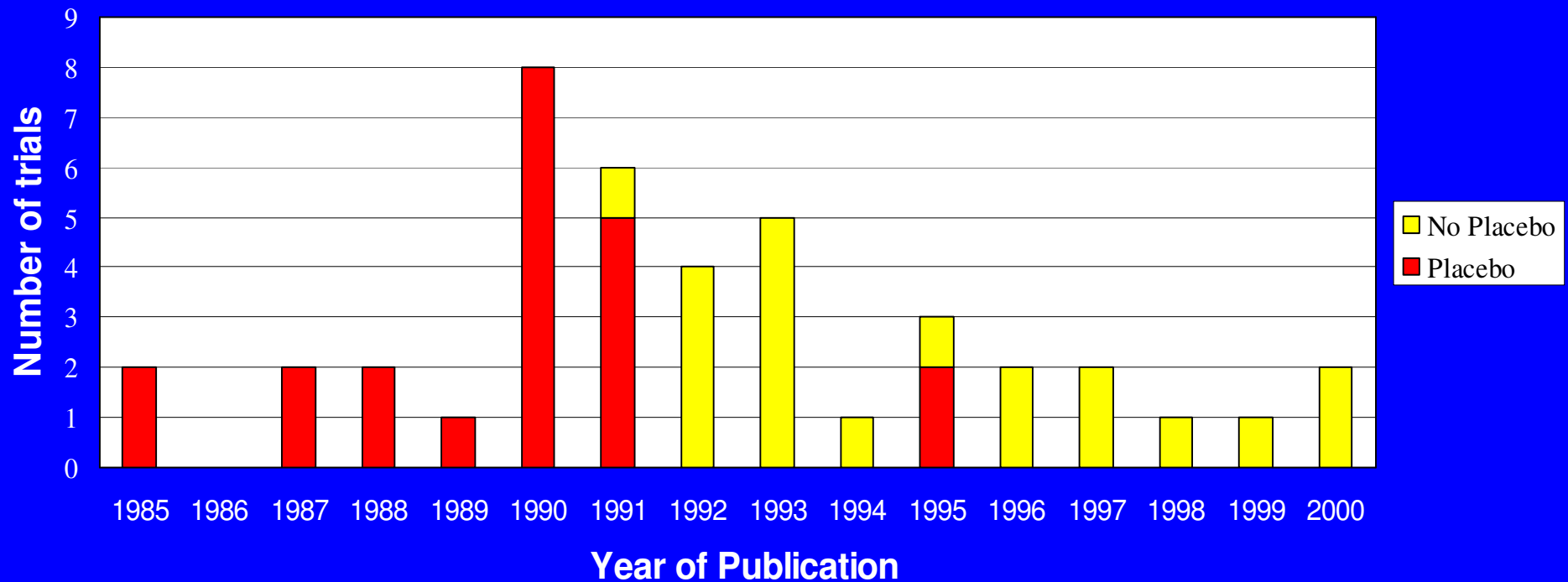
# A Drug Company-sponsored Unethical Clinical Trial in Developing Countries

- Discovery Laboratories, Doylestown, PA
- Synthetic surfactant (Surfaxin); 4 surfactants approved since 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

- 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



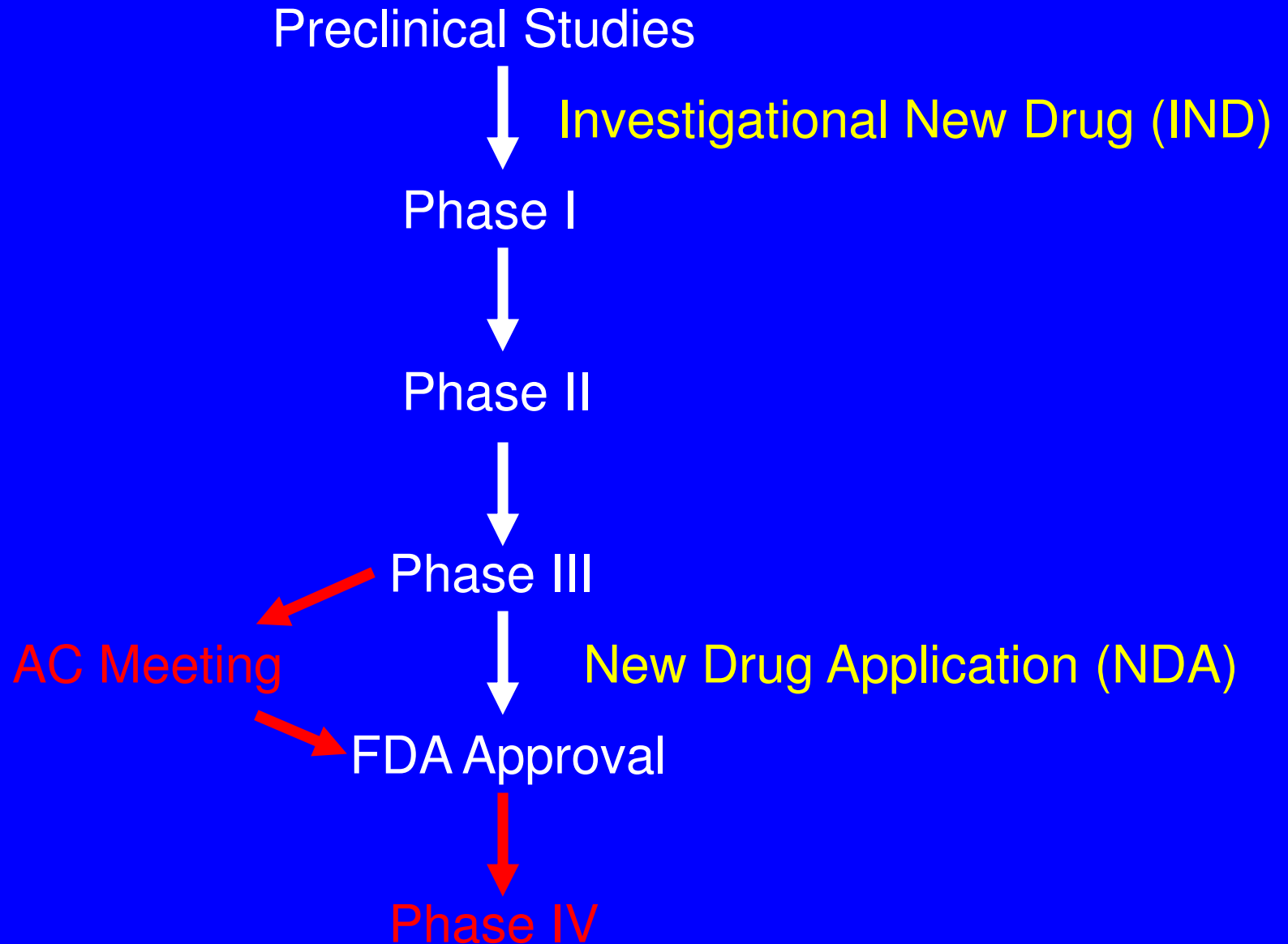
# U.S. Exceptionalism (Partial Listing)

- Landmine treaty
- Kyoto treaty
- International Criminal Court
- Convention on the Rights of Women
- Anti-ballistic weapons treaty
- Geneva Convention
- War in Iraq (ask Kofi Annan)
- Declaration of Helsinki

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# FDA Drug Approval Process



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# Phase I GMPs

- 2006: FDA proposes exempting drugs in Phase I from rigorous GMPs
- Rationale: “to streamline and promote the drug development process while ensuring the safety and quality of [drugs for use in] Phase 1 clinical trials.”
- 2008: Proposal finalised

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# Disclosed Conflict Rates for FDA AC Members, 2001-4

|                                  | Through<br>January 2002 | After<br>January 2002 | Total |
|----------------------------------|-------------------------|-----------------------|-------|
| Per meeting COI<br>rate*         | 77%                     | 72%                   | 73%   |
| Per person-meeting<br>COI rate** | 28%                     | 28%                   | 28%   |

Recusal rate: 1%

\*Percentage of 221 meetings where at least 1 COI was disclosed

\*\*Percentage of 2947 AC member or consultant person-meetings disclosing a COI

Source: JAMA 2006;295:1921-8

# Relationship between Conflict Type and Voting Behavior

|  | Index Conflict   | Competitor Conflict | Any Conflict     |
|--|------------------|---------------------|------------------|
| Continuous outcome                     | NS               | NS                  | NS               |
| Dichotomous                            | NS               | NS                  | NS               |
| Exclusions lead to less favorable vote | 64%              | 77%                 | 72%              |
| Exclusions change vote outcome         | No               | No                  | No               |
| Mantel-Haenszel                        | 0.74 (0.39-1.39) | 1.20 (1.12-1.28)    | 1.10 (1.03-1.17) |
| Monte Carlo                            | NS               | P<0.05              | NS               |

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# Clinical Trials Registries

- Registries
  - Recruitment
  - Protocol adherence
  - Publication bias
- Results databases
  - Respect for patients
  - Meta-analyses

# Clinical Trials Registries

- Survey of all registries worldwide
- July 2007
- Public registries:
  - [Clinicaltrials.gov](http://Clinicaltrials.gov)
  - ISRCTN
  - ACTR
  - NTR
- Excluded:
  - Japanese registry
  - Portals
  - Disease-specific registries

# Clinical Trials Registries

|                                   | Public (n=4) | Private (n=18) |
|-----------------------------------|--------------|----------------|
| Clinical Trial Registries         | 4            | 13             |
| Open to All Registrants           | 4            | 2              |
| Verification                      | 4            | 2              |
| Not-For-Profit                    | 4            | 0              |
| Results Databases                 | 0            | 17             |
| Registry and Results Database     | 0            | 12             |
| Stipulate Essential Data Elements | 0            | 8              |
| Detailed Outcome Information      | 0            | 6              |
| Results Posted Within 12 Months   | 0            | 7              |

Source: <http://www.citizen.org/publications/release.cfm?ID=7534>

# FDA Legislation, 2007

- Clinicaltrials.gov expanded to include results
- Deferred for subsequent study:
  - Lay summary
  - Posting of studies on unapproved products

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# OTC Cough and Cold Remedies

- Decongestants, antihistamines, antitussives, expectorants
- >800 products on the U.S. market
- Used by 10% of U.S. children each week
- 12 clinical trials since 1950s
  - None show evidence of efficacy (0-12 years)
- 123 deaths reported to FDA since 1969
- Voluntary industry ban for <2 year olds
  - 1/3 of products on shelves recommend this

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# Vagus Nerve Stimulator

- Approved for epilepsy; approval sought for treatment-resistant depression
- Randomized, controlled trial: 15% vs. 10% response rate at 12 weeks (NS)
- Non-randomized, non-concurrent, unblinded: 30% vs. 13% response rate at 2 years on 2<sup>o</sup> outcome (P<0.05)
- 2004: FDA scientists overrule favorable AC vote
- 2005: Device Center chief signs approval letter
- 2006: Senate Finance Committee investigation shows all 20 reviewing scientists opposed approval
- 2007: CMS denies reimbursement

# Collagen Scaffold

- Inserted into knee during arthroscopic meniscectomy
- Effectiveness claimed based on laboratory data
- RCT for patients with 1-3 prior surgeries
  - No efficacy on all 3 primary endpoints
  - Higher rates of reoperation
- FDA Advisory Committee votes 6-1 for approval

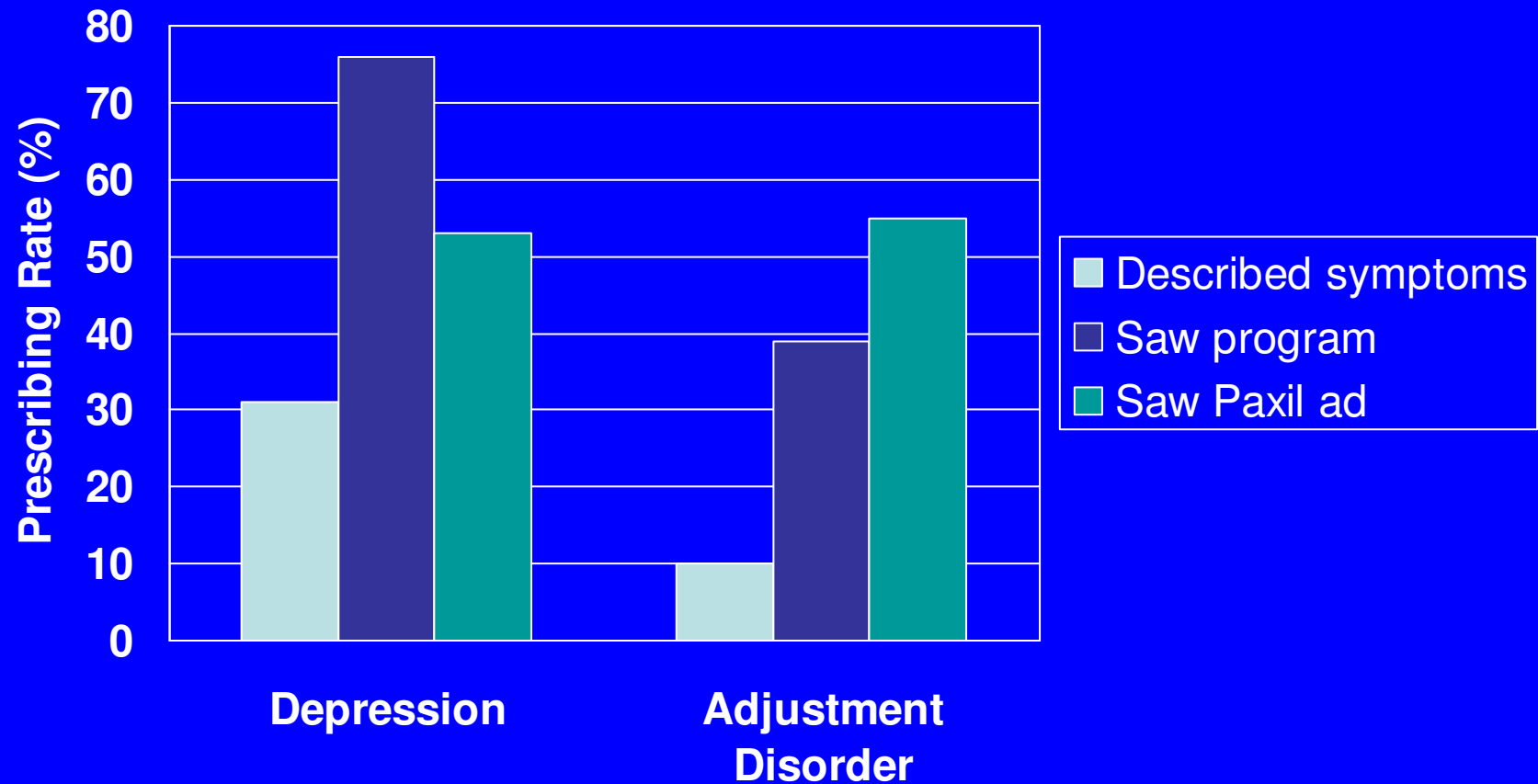
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# Direct-to-Consumer Advertising

- Potential Risks
  - DTC advertisements bear little relationship to public health needs
  - Many DTC advertisements are misleading or dangerous
  - Doctors are being coerced to prescribe
  - The price of health care is being driven up
- Potential Benefits
  - Undertreated conditions might be treated
- Can the Benefits be Otherwise Obtained?

# Prescribing of Antidepressants To Standardized Patients



Source: JAMA 2005;293:1995-2002

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# Off-label Promotion

- 21% of all prescribing; 73% without scientific basis
- Prior to 1997: complete ban
- 1997: Can distribute peer-reviewed RCTs
  - Must be pre-reviewed by FDA
  - Company must submit clinical trial protocol to FDA within 6 months
- 2006: statute lapses
- 2008 proposal: no pre-review or clinical trial requirement

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# Changes Being Effected Supplements

- Companies' ability to change label unilaterally
- 2008 Final Rule:
  - “Causal association”
  - “Newly acquired information”
  - “reasonable time period”
- Relationship to preemption of state lawsuits
- Wyeth v. Levine