PDUFA & FDA Legislation

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Marc Wilenzick, Pfizer
Dan Kracov, Arnold & Porter
Dan Carpenter, Harvard Dept. of Government

Disclaimer

The views expressed in this presentation are offered for discussion purposes only; the panel members are speaking as individuals and not on behalf of the government, industry, or any individual organization.

Agenda

- Prescription Drug User Fee Act (PDUFA)
- Enzi-Kennedy Legislation
- Improving Risk Management

Background on PDUFA

- PDUFA was established in 1992 to expedite FDA's drug & biologic reviews.
- PDUFA was extended in 1997 as part of the *FDA Modernization Act* and again in 2002 as part of the *Public Health Security and Bioterrorism Preparedness and Response Act.*
- User Fees: Under PDUFA, FDA collects application fees, establishment fees, and product fees, which it can spend on staffing and support for its review of human drug applications.
- FDA considers PDUFA to be "the cornerstone of modern FDA drug review…" Reference: http://www.fda.gov/oc/pdufa/PDUFAWhitePaper.pdf

More Background on PDUFA & Its *Impact*

- Since 1992, FDA has nearly doubled its NDA review staffing (from 1,277 FTEs to 2,503 FTEs in 2004) and reduced review times.
- Median review time for priority applications improved from 13.2 months (1993) to 6.4 months (2003)
- Median review time for human drugs generally also decreased, from 22.1 months to 13.8 months.
- The volume of new drug applications, efficacy supplements, manufacturing (CMC) supplements, and adverse event reports have increased considerably over the same period (up 50%, 80%, 400%, and 80%, respectively, since 1993).

Reference: http://www.fda.gov/oc/pdufa/PDUFAWhitePaper.pdf

Background on PDUFA

- Over half of FDA's funding for the review of human drug applications comes from PDUFA. The 2006 fee for review of an NDA is $767,400.

- PDUFA III will expire in October 2007. The Medical Device User Fee Act (MDUFA), the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) also expire in October 2007.

- 2006 Device User Fees are 260k for a PMA, 4k for a 510(k), with reduced fees for firms with sales of less than $100M. Fees also are in place for mammography inspections, animal drug reviews, & color certification fees. FDA has proposed to charge user fees for GMP re-inspections and food & animal feed exports.

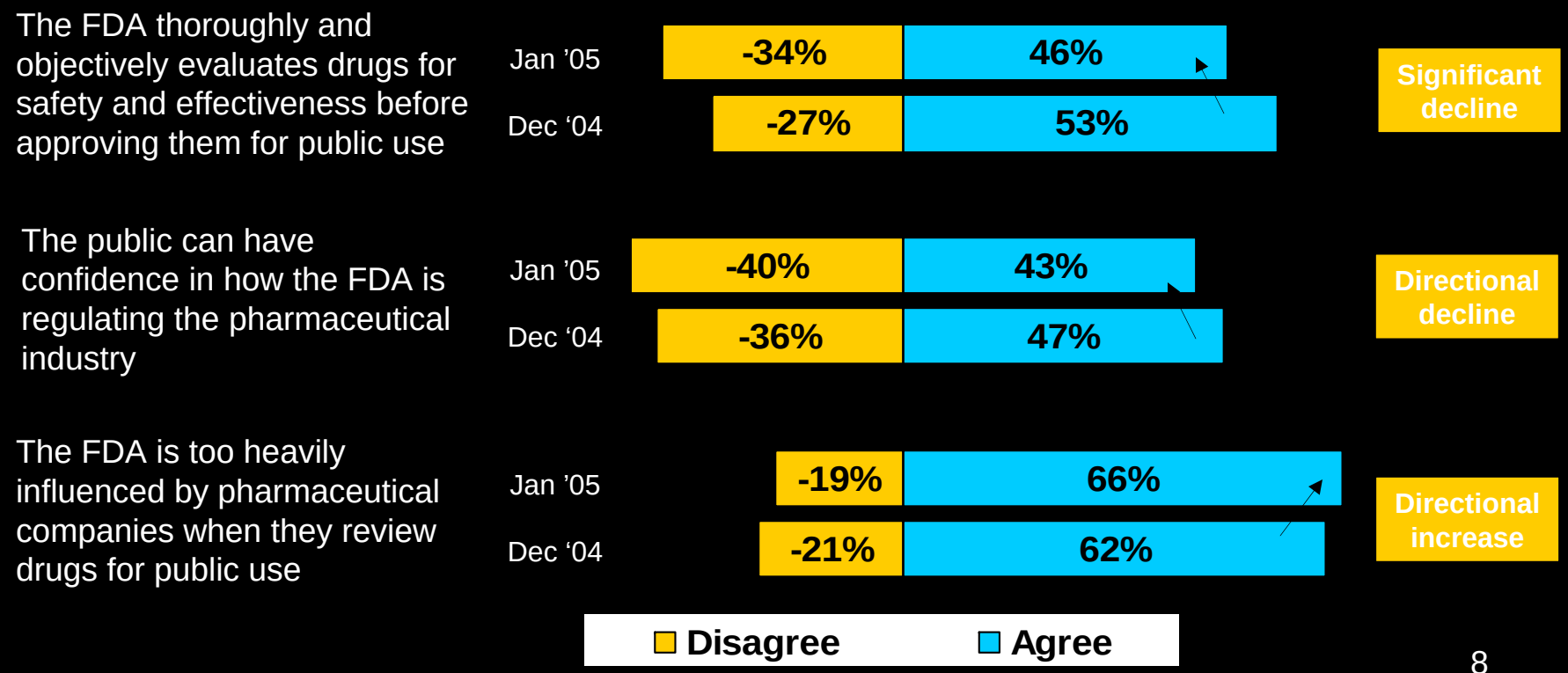
"The suspicion … is that the user fee payers only agree to fund what they perceive as being most helpful to themselves, and only for so long as it is helpful to their interests. The implicit threat is that they might be less willing to pay if things at FDA begin to drift…"

- FDA Webview (April 10, 2006)
  http://www.fdaweb.com/login.php?sa=v&aid=D5102462&cate=&stid=%241%244x3.5I%2F.%24AjQFC8SUvCrQtHIZq647S0

Confidence in FDA

FDA is thorough? Public can have confidence?
Fewer than half agree.

<u>FDA too heavily influenced by industry? Two in three agree</u>.

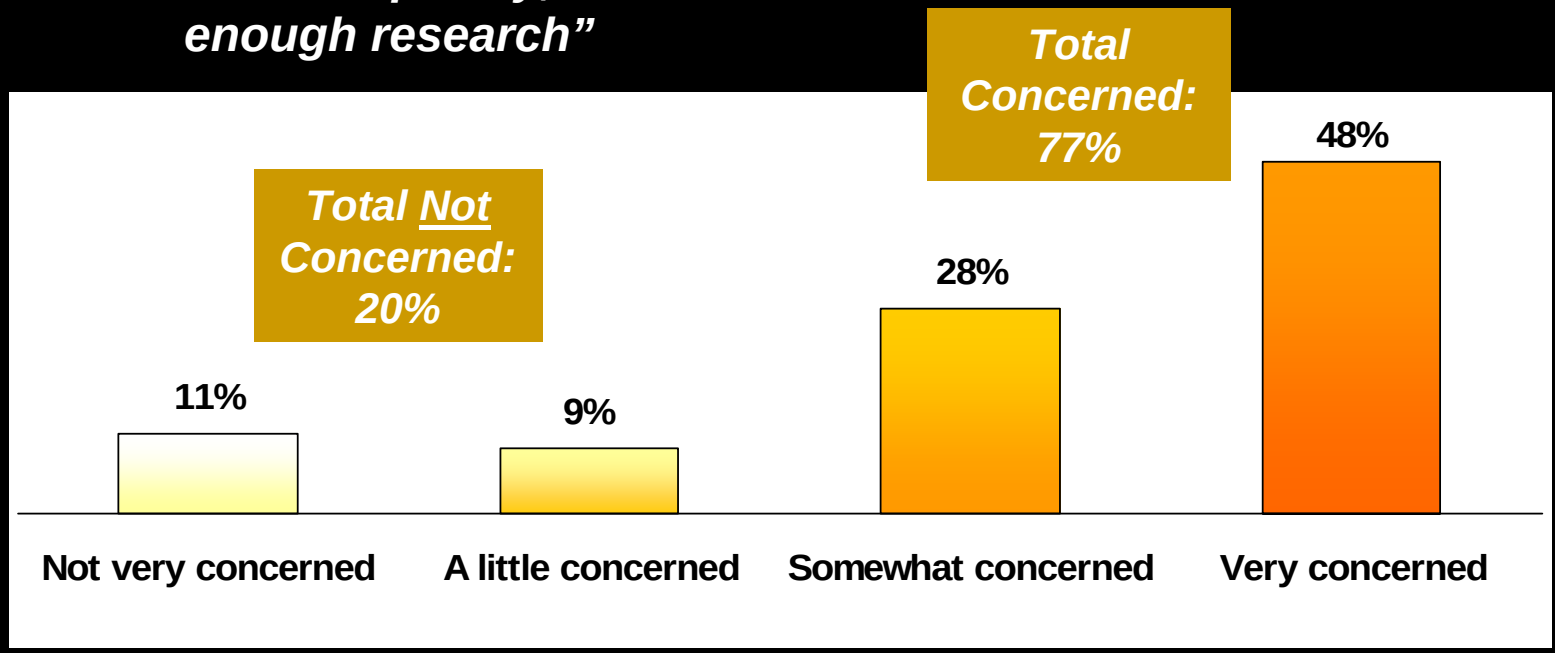


January 2005 Research

Is FDA Approving Medicines Too Quickly?

I am going to read you a list of things that concern some people and I'd like to know how concerned you personally are about each one—very concerned, somewhat concerned, a little concerned or not very concerned about.

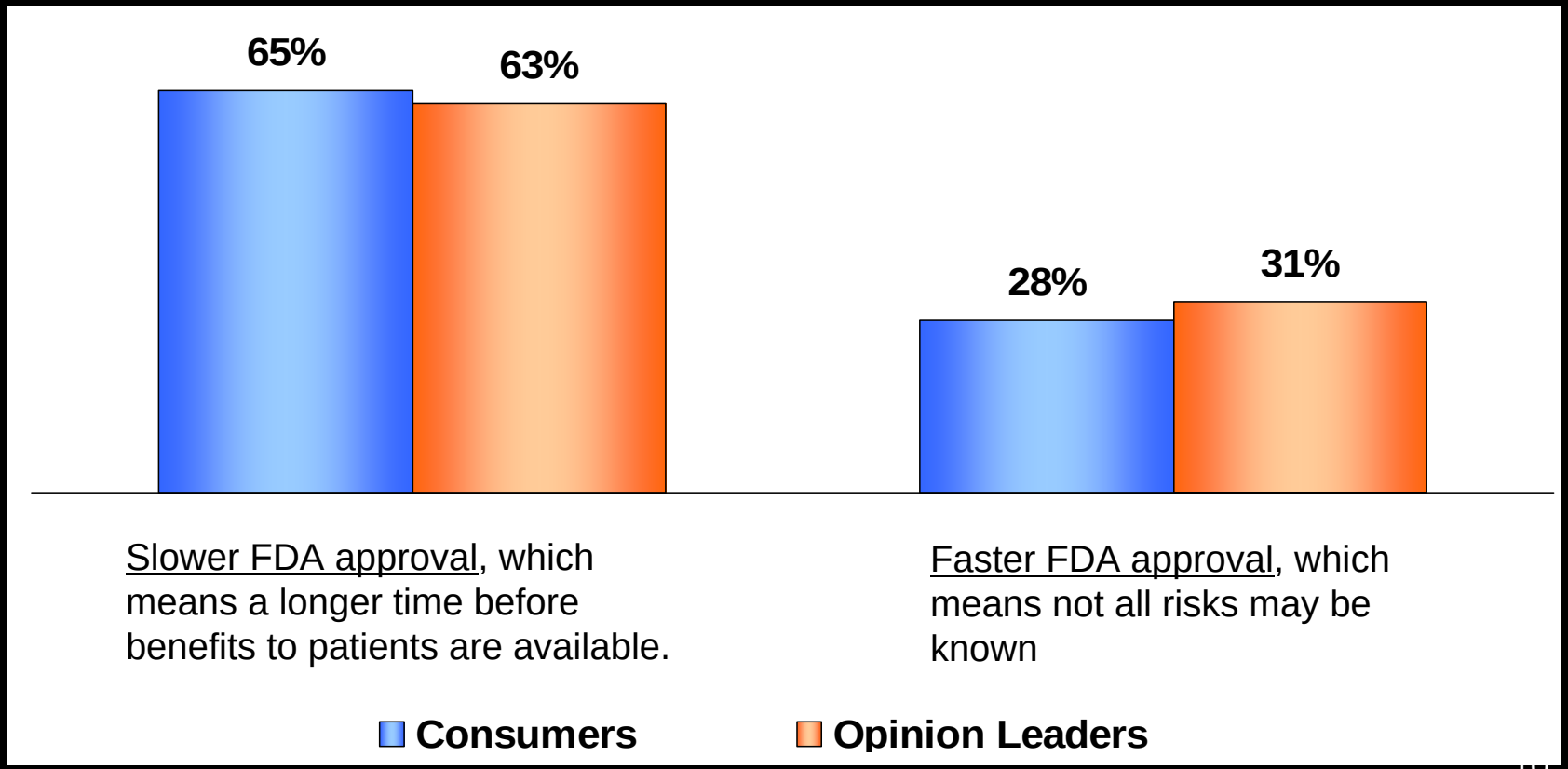
"That the FDA is approving medicines too quickly, without enough research"



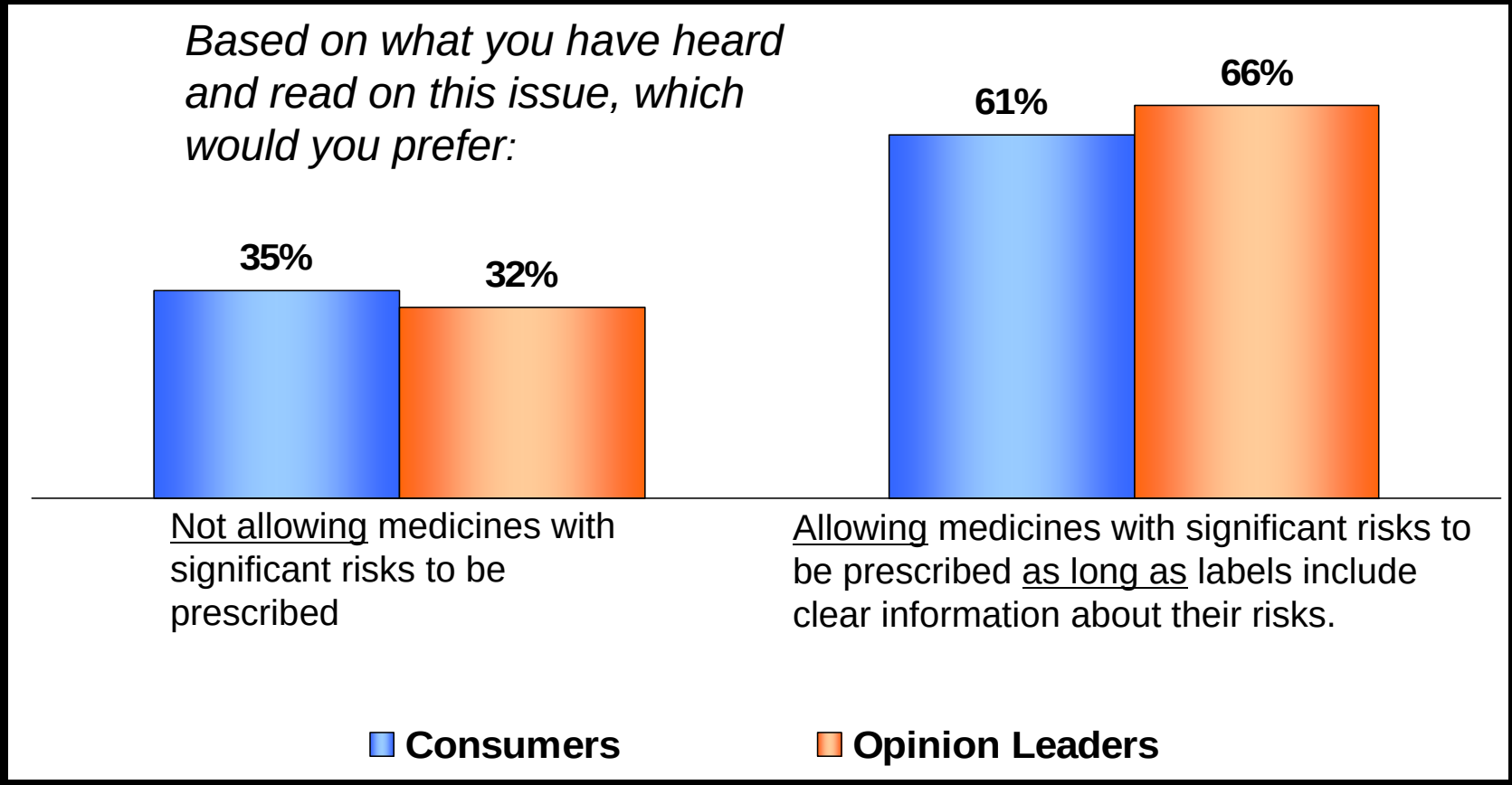
(Opinions among opinion leaders are about the same.)

Consumers Prefer Slower Approvals if it Means More Risks are Known

If a medicine offers real benefits to patients, which would you prefer:



Consumers Prefer Accepting Risk Over Keeping Riskier Medicines Off the Market



User Fees and FDA New Drug Review: Analysis and Policy Options

Daniel Carpenter

Professor of Government, and
Director, Center for American Political Studies (CAPS)
Department of Government
Faculty of Arts and Sciences
Harvard University

FDA Symposium
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PDUFA

Assume all here know, but…

(1) Per-application tax on sponsors, most proceeds to "buy" NDA reviewers

(2) Lots of other things in the legislation (FDAMA – "micromanagement," conferences)

(3) Crucial mechanism: review time goals, or deadlines, a.k.a. "PDUFA clocks."

Why Acceleration?

Lots of things have been happening

(1) Faster government (part management, part politics)
(2) More people
(3) Pressure for disease advocacy groups
(4) Changing culture at FDA? [Possibly; many here would know better than I would]

Empirical Study

Focus on review-specific deadlines. Use flexible and general statistical approach to address two questions:

Q1: Have PDUFA clocks changed FDA review behavior? Assess changes in behavioral review cycle before versus after deadline;

Q2: Have PDUFA clocks changed outcomes of FDA decision making? Assess whether changes in decision patterns have been associated with different policy outcomes.

KEY: need flexible deadline, so can observe post-deadline choices

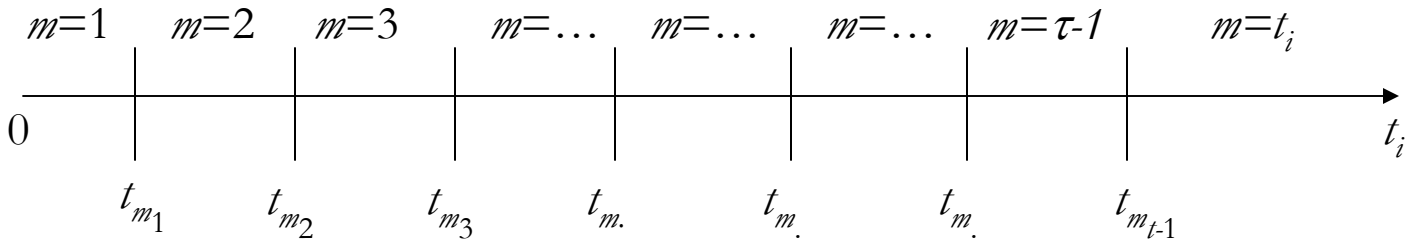
Clocks by Statute

PDUFA, 1992 (began 9/1992): by 1997, review and act upon 90% of standard drugs in 12 months, 90% of priority drugs in 6 months.

FDAMA, 1997 (began 10/1997): by FY 1999, 30% of standard drugs in 10 months, by FY 2002 90% of standard drugs in 10 months; same as PDUFA for priority drugs.

"PDUFA III," 2002 (began 10/2002): For standard and priority drugs, same deadline months as in FDAMA.

Method for Q1:
Partition Review Time by Relevant Intervals



Modification of Cox proportional hazards model;
can estimate several review cycles at once.

Semi-parametric Approval Hazard Ratio (AHR) estimates, by user-fee regime, non-priority NMEs

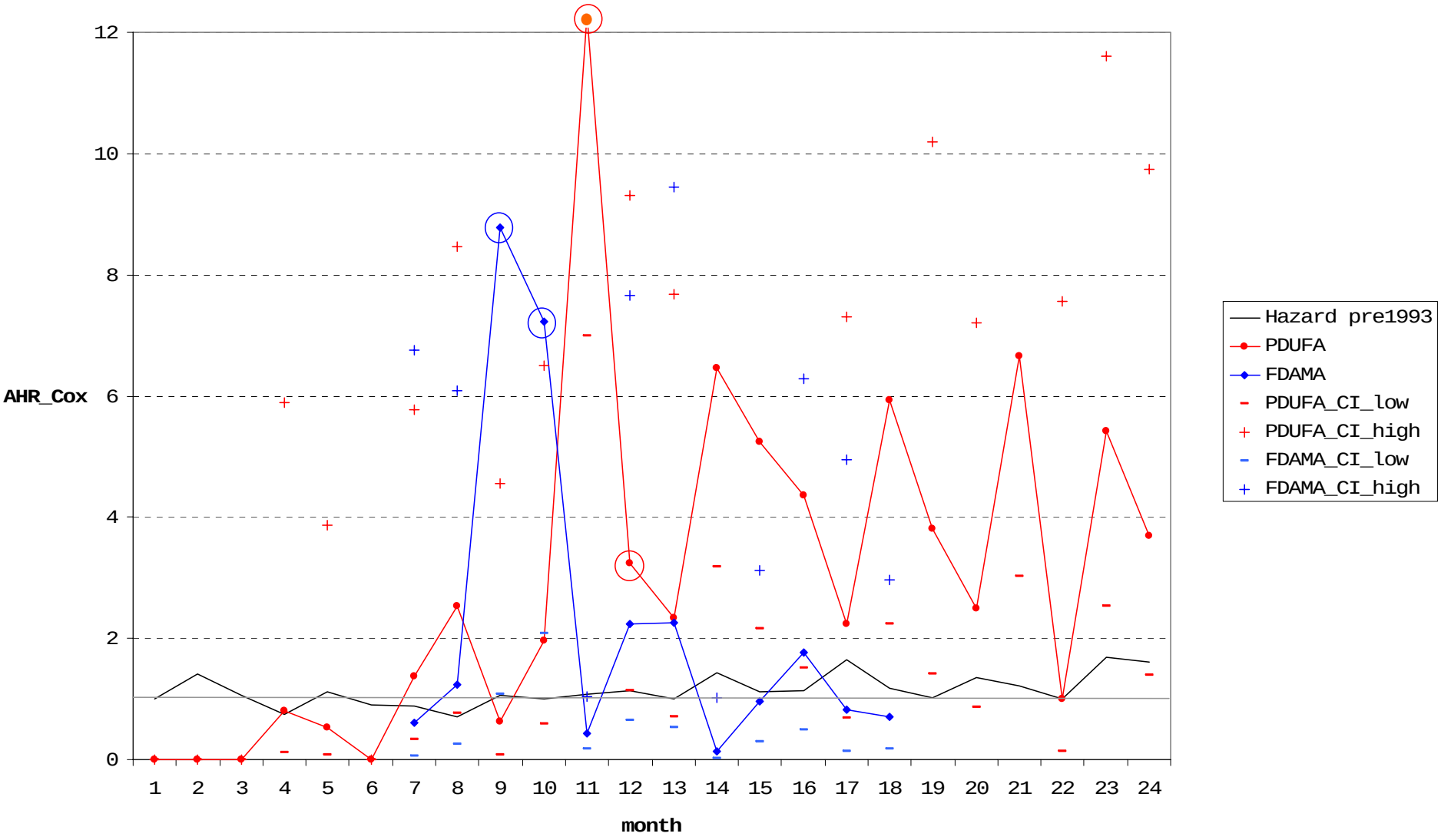
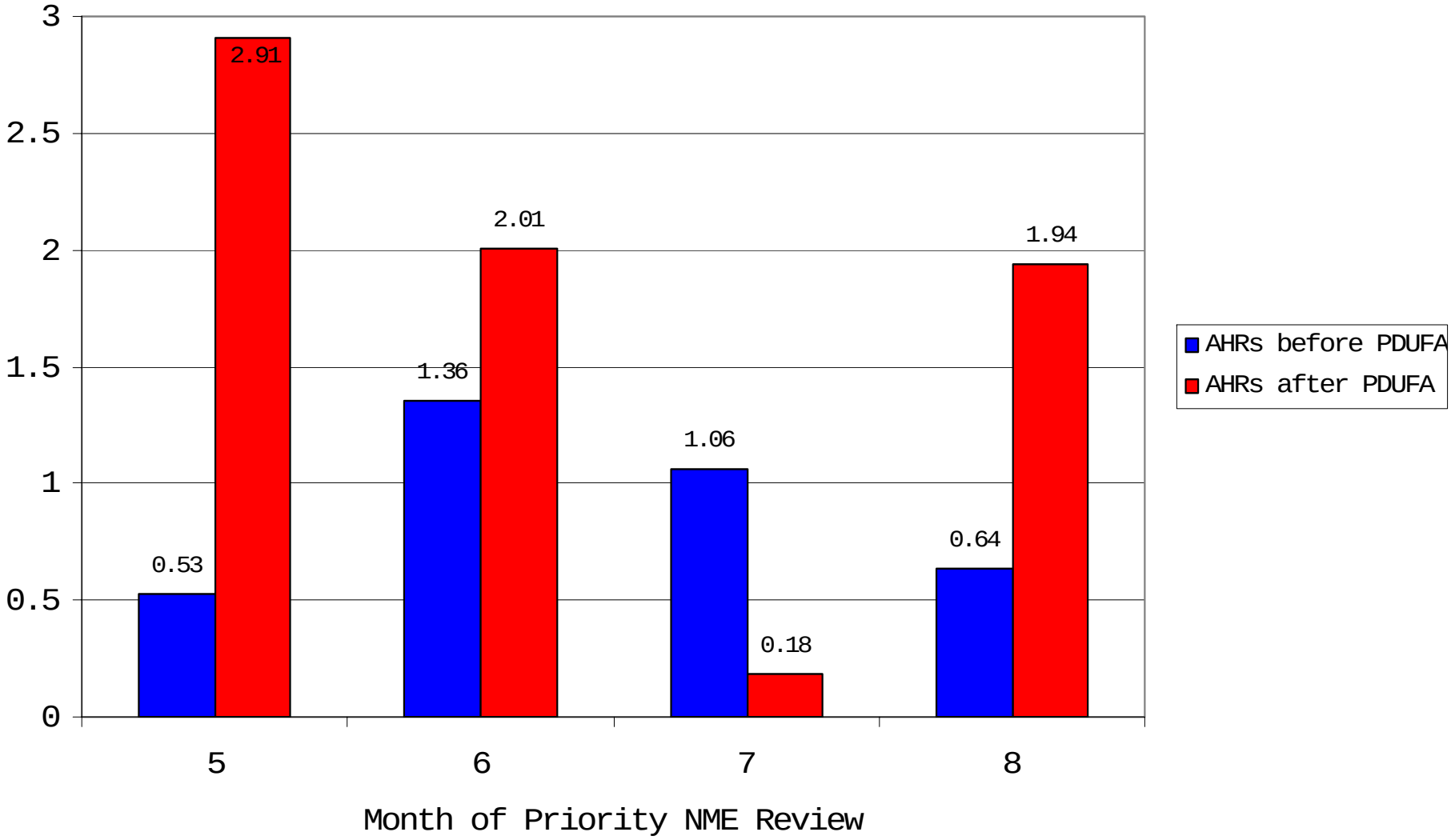


Figure 2: Approval Hazard Ratios for Priority NMEs, before and after PDUFA



Empirical Question 2: Compare "Outcome" Measures for Approvals before and after Deadline

- Gather data on post-marketing regulatory events (PMREs) (withdrawals, black-box warnings, etc.)
- Compare PMRE rates for drugs approved before versus after deadline.
- Use nearest-neighbor matching techniques to balance samples.

Figure 3: Ratio of Increase in Post-Marketing Regulatory Event (PMRE) Rate, before versus after statutory deadline, Non-Priority NMEs

[bars are multipliers with 95% upper confidence interval shown]

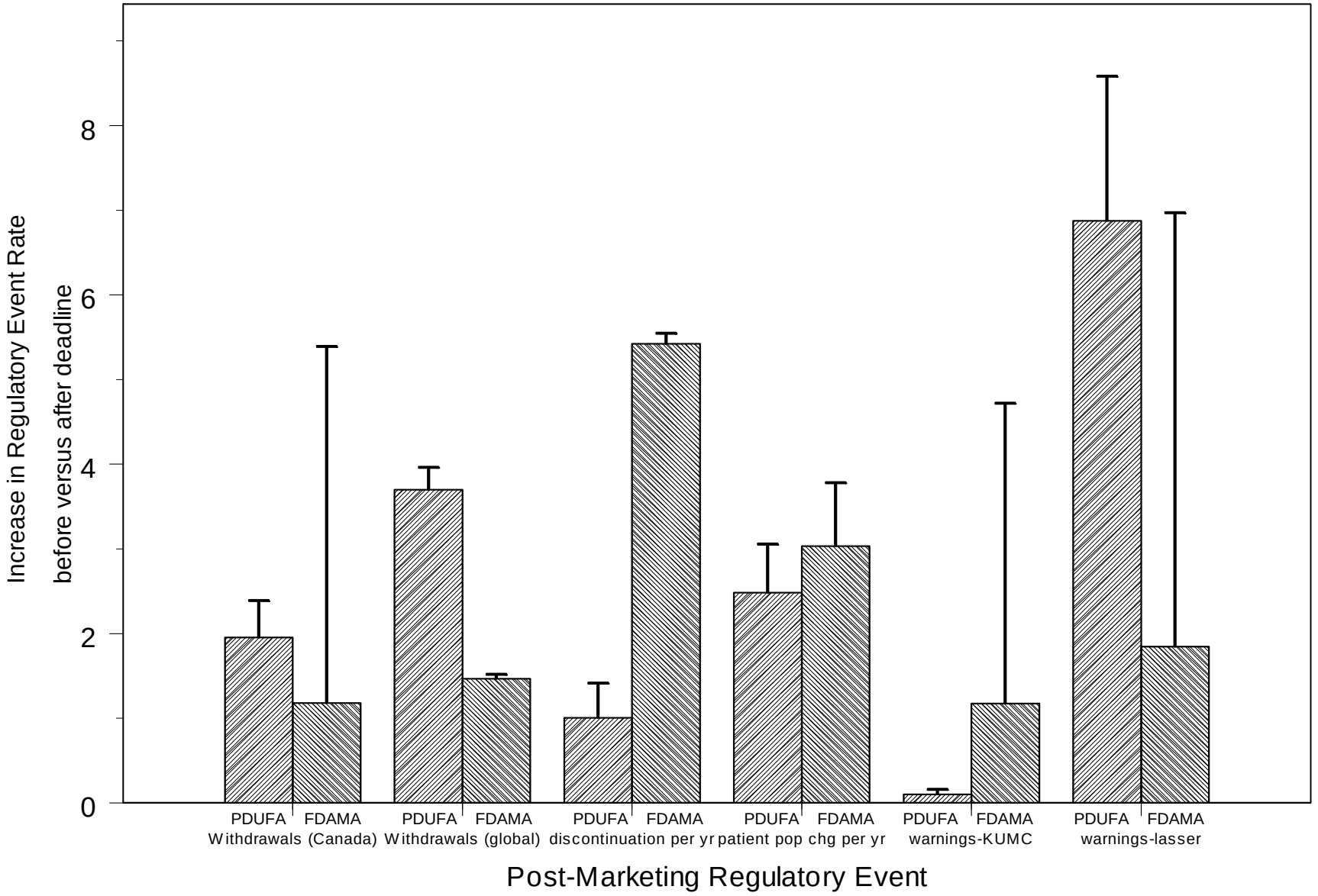


Table Z5: Results from Nearest-Neighbor Matching Analyses				
	Withdrawal	Lasser	KUMC	Discont
ATE – pdufa1112 [N = 481]	0.4462 (0.1003)	0.6677 (0.2089)	3.5973 (0.5791)	0.9076 (0.1570)
ATE-fdama0910 [N = 481]	-0.0311 (0.0489)	-0.0599 (0.0671)	0.3470 (0.3954)	-0.9556 (0.3105)
ATE-pdufa0506-priority [N = 85]	-0.0458 (0.0570)	-0.0353 (0.0527)	0.1306 (0.3285)	0.0583 (0.0245)

Conclusions

1. Still under revision; tentative.
2. Policy implications: Deadlines for regulatory decision need further scrutiny [FDA user-fee act up for reform in 2007].
3. Are there other ways of accelerating regulators?
4. Theoretically, need model of dynamic optimization in organizational or network context (might explain piling in penultimate period).

Modest Proposal-Carpenter

Why Not Harness User Fees for Drug Safety?

(1) Increase per-application fees by a tax, spend $ on RCTs and epidemiological data, plus FDA K investments for safety
(2) Would probably help FDA reputationally.
(3) Would help PhRMA, industry politically.
(4) If FDA/NIH conducts studies, less legal liability for firms (who can't have "known ahead of time" about postmarket risks)
(5) Would increase funding for 'post-market' safety research, currently quite low.

S. 3807: Enzi-Kennedy Bill

109TH CONGRESS
2D SESSION

S. _____

To amend the Public Health Service Act and the Federal Food, Drug, and Cosmetic Act to improve drug safety and oversight, and for other purposes.

IN THE SENATE OF THE UNITED STATES

_____

_____ introduced the following bill; which was read twice and referred to the Committee on _____

A BILL

To amend the Public Health Service Act and the Federal Food, Drug, and Cosmetic Act to improve drug safety and oversight, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.

This Act may be cited as the "Enhancing Drug Safety and Innovation Act of 2006".

FDA Reform / Enzi-Kennedy Legislation

1. Title I: Risk Evaluation and Mitigation Strategy (REMS)
2. Title II: Reagan-Udall Institute for Applied Biomedical Research
3. Title III: Clinical Trial Registration & Results Database
4. Title IV: Conflicts of Interest – Advisory Committees

Enzi-Kennedy: REMS

- Required for all new NDAs, BLAs, certain supplements
- FDA can require for certain approved products, or treat existing restrictions as a REMS (e.g., Subpart H products)
- Funded by user fees
- Negotiated by Sponsor and FDA

Enzi-Kennedy: REMS

- REMS Mandatory Elements
  - »Labeling
  - »Reporting of adverse events
  - »Pharmacovigilance statement addressing whether additional surveillance or studies are required
  - »Timeline for periodic assessment of the REMS
    - » At least annually for the first 3 years

Enzi-Kennedy: REMS

- Optional Elements
  - » MedGuide and/or patient package insert
  - » Communication plan
  - » Post-approval studies
  - » Advertising restrictions
    - » Preclearance
    - » Mandated disclosures
    - » Moratorium of up to 2 years on direct-to-consumer advertising of newly marketed product
  - » Restrictions on use or distribution
    - » Must be commensurate with the risks of the product, necessary to ensure safe use, and not unduly burdensome on patient access

Enzi-Kennedy: REMS

- Sponsor bears responsibility to ensure compliance with REMS restrictions
  - »Including limiting participation of non-compliant health care providers, pharmacists, etc.
- Dispute Resolution
  - »Divisional level reviews in accordance with PDUFA performance goals
  - »Sponsor can request Drug Safety Oversight Board review – not binding on the Secretary
- Civil Penalties

Enzi-Kennedy: REMS

- Drug class effects
- Harmonization
- No effect on labeling changes that currently do not require pre-approval
- Generics must comply with REMS, with the exception of post-approval clinical trial requirements
- Establish searchable repository of approved labeling
- Report to Congress on strategic plan on FDA information technology

"… one FDA official, who asked not to be named, is rejecting this [REMs] proposal. The REMS program unnecessarily slows the drug review process, removes agency discretion to tailor risk management reviews for individual drugs and places unreasonable deadlines and financial burdens on the agency, the source said. These concerns are shared by a number of other FDA officials, the source added. "The timelines for achieving goals under the legislation are unrealistic, and the resources that it would require would add significant new burdens and financial strains on FDA…". "It's a very bureaucratic solution to a very practical problem."

"… these comments are merely "pot shots from faceless, nameless FDA talking heads," --- Enzi spokesman

--FDA News (August 14, 2006)
http://www.fdanews.com/wdl/38_32/capitolhill/58860-1.html

Enzi-Kennedy: Reagan-Udall Institute

- Intended to advance Critical Path Initiative to modernize development and evaluation of drugs, devices, and biologics
- $20 million authorized for 2008-2013, plus industry “donations”
- Board of Directors
  - »Industry, Government, Academia, Patients, Providers

FDA Reform / Enzi-Kennedy Legislation

- What is good about the proposal?
- Areas of greatest impact to development, approval, and commercialization?
- Problems, if any, with the proposal?

Panel Discussion

Status of issues that *need* to be addressed as part of FDA/PDUFA:

- Status of User Fee Reauthorization/Change
- Impact of Drug Safety on PDUFA Legislation
- FDA Resources and if/how PDUFA might help
- Other Issues?

  (E.g. generics, follow-on biologics, state tort preemption, clinical trial registries/databases, conflicts of interest, etc.)

Questions?

Comments?