WORKSHOP ON POTENTIAL CONFLICT OF INTEREST IN GRAS ADDITIVE DECISIONS
AUGUST 7, 2013 AT THE PEW CHARITABLE TRUSTS

Background
In December 28, 2010, the U.S. Food and Drug Administration (FDA) requested comments on potential guidance regarding conflicts of interest (COI) when someone other than the agency makes a "generally recognized as safe" (GRAS) determination that an additive is safe for use in food. FDA acted in response to a recommendation by the U.S. Government Accountability Office in 2010 that the agency develop a strategy to minimize the potential for COI in company's GRAS determinations.

Workshop objectives
Explain the concerns that have been raised regarding the potential for COI in GRAS self-determinations, and identify and discuss approaches to resolving those concerns. Receive and discuss comments on proposed draft guidance on the issue.

Agenda

8:30 a.m. **Registration and continental breakfast**

9:00 **Welcome and introductions**
- Facilitator: Paul De Morgan, RESOLVE
- Presenters: Erik Olson, The Pew Charitable Trusts
  Tony Pavel, Morgan, Lewis & Bockius LLP (representing Institute of Food Technologists)

9:20 **Potential conflicts of interest in GRAS determinations: What are the concerns**?
- Moderator: Joe Hotchkiss, Michigan State University
- Presenters: Tom Neltner, The Pew Charitable Trusts
  Sheldon Krimsky, Tufts University
  Jim O'Reilly, University of Cincinnati

Question and answer session: 10 minutes

10:00 **Agency expert panels: Approaches to conflicts of interest when interests are disclosed**
- Moderator: Vincent Hegarty, Michigan State University
- Presenters: Alberto Spagnolli, European Food Safety Authority
  Jill Hartzler Warner, U.S. Food and Drug Administration

Question and answer session: 15 minutes

11:00 **Break**

11:15 **What are the factors that may result in undue influence?**

- Moderator: Gail McCarver, Medical College of Wisconsin
- Presenters: Sunita Sah, Georgetown University and Harvard University
  Sheldon Krimsky, Tufts University

Question and answer session: 20 minutes

12:30 p.m. **Lunch** (provided)

1:15 **Practitioners' perspective: what makes GRAS different?**

- Moderator: Steve Roberts, University of Florida
- Presenters: Nancy Rachman, NJ Rachman Consulting
  Martin Hahn, Hogan and Lovells
  Tony Pavel, Morgan, Lewis & Bockius LLP

Question and answer session: 15 minutes

2:15 **Break**

2:30 **Trade association approaches to conflicts of interest**

- Moderator: Glenn Sipes, University of Arizona
- Presenters: Leon Bruner, Grocery Manufacturers Association
  John Hallagan representing Flavor and Extract Manufacturers Association

Question and answer session: 15 minutes

3:30 **Comments on key issues raised in potential guidance**

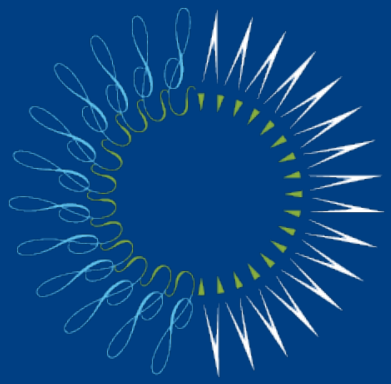
- Facilitator: Paul De Morgan, RESOLVE
- Moderator: Tom Zoeller, University of Massachusetts at Amherst
- Presenter: Tom Neltner, The Pew Charitable Trusts

Question and answer session: 45 minutes

4:30 **Wrap-up**

- Facilitator: Paul De Morgan, RESOLVE
- Moderator: John Vandenbergh, North Carolina State University

4:45 **Adjourn**



THE PEW CHARITABLE TRUSTS

Conflicts of Interest in Approvals of GRAS Additives: Out of Balance

Tom Neltner

Project Director, Food Additives Project
The Pew Charitable Trusts

Overview

- Introduction to food work at the Pew Charitable Trusts
- Summary of work by Pew's Food Additives Project
- Discussion of FDA's Generally Recognized as Safe (GRAS) Exemption
- Review of conflicts of interest (COI) in GRAS decision making
- Conclusions

Pew's approach to food

- Science-based policies
- Pragmatic, effective solutions
- Transparency
- Engage all stakeholders

Food-related projects at Pew

- Food Safety Project
  - FDA Food Safety Modernization Act
  - Meat & poultry investigation
- Kids Safe and Healthful Foods
- Human Health and Industrial Farming

Food Additives Project

- Launched in 2010:
  - Comprehensive analysis of regulatory program/science
  - Develop evidence-based policy recommendations
- Transparent process engages industry, academic, government and public interest stakeholders
- Workshops and articles, primarily in peer-reviewed journals

Workshops held by Pew

- Cosponsored by *Nature* and Institute of Food Technologists (IFT)
- Hazard assessment – April 2011
- Exposure assessment – November 2011
- Policy options – April 2012
- Dose response for endocrine disruptors – April 2012
- Potential conflicts of interest in GRAS additive decisions – August 2013

Articles authored by Pew

- *Navigating the U.S. Food Additive Regulatory Program* – 2011
- *Hazard Assessment Workshop Proceedings* – 2011
- *Exposure assessment Workshop Proceedings* – 2013
- *Looking Back to Look Forward: A Review of FDA's Food Additives Safety Assessment and Recommendations for Modernizing its Program* – June 12, 2013
- *Data Gaps in Toxicity Testing of Chemicals Allowed in Food in the U.S.* – In Press
- *Conflicts of Interest in Approvals of Additives to Food Determined to be GRAS: Out of Balance* – August 7, 2013
- Capstone Report – Expected August 2013

Related research supported by Pew

- Evaluation of food additive issues by American Academy of Pediatrics (AAP)
- “NanoRelease Food Additives” project at International Life Sciences Institute (ILSI) Research Foundation
- “Endocrine Active Chemicals: Science to Practice” workshop by National Institutes of Health and European Commission
- Review of regulation and safety assessments outside the U.S. by Berna Magnuson and Cantox International
- “Chemical Testing in the 21st Century” workshop by the Environmental Defense Fund

Basics

- ~ 10,000 chemicals allowed to be added to food
- ~ 3,000 not reviewed by FDA
- ~ 1,000 unknown to FDA

Concerns about GRAS & implications for FDA's science and reassessment of old decisions

Generally Recognized as Safe (GRAS) exemption

- In 1958 Congress exempted use of GRAS additives from Food Additive Petition requirement
- FDA allows manufacturers to make GRAS safety determinations without notifying the agency
- Since 1997, FDA has encouraged voluntary notifications of GRAS determinations. FDA review results in:
  - No questions letters
  - Insufficient basis letters
  - Cease to evaluate letters
- Over the past 10 years, GRAS Notifications outnumber Food Additive Petitions by more than 14 to 1 for direct additives

2010 GAO GRAS Report

- "One of FDA's principal missions is to ensure the safety of the nation's food supply, but a growing number of substances that companies have determined are GRAS may effectively be excluded from federal oversight."
- "However, FDA may be constrained in detecting any such future problems because it lacks information about an unknown number of substances companies have determined to be GRAS without informing the agency."
- "[W]ithout issuing guidance on how to prevent conflicts of interest and information in companies' GRAS notices regarding expert panelists' independence, FDA has less assurance of the independence of the experts companies employ to support their GRAS determinations."

Conflicts of interest: GAO Recommendation #4

- **Recommendation:** Develop a strategy to minimize the potential for conflicts of interest in companies' determinations.
- **Status:** As of May 2012, FDA has not decided what, if any, actions it will take.
- **FDA comments:**
  - Requested comments on several GAO recommendations on December 28, 2010
  - Reviewing comments received

Conflicts of Interest in Approvals of Additives to Food Determined to be GRAS: Out of Balance

- *Journal of American Medical Association Internal Medicine*
- Available on-line on August 7, 2013
- Authors
  - Tom Neltner, Heather Alger and Maricel Maffini of Pew
  - Lisa Bero of University of California San Francisco
  - Sheldon Krimsky of Tufts University
  - James O'Reilly of University of Cincinnati
- Evaluates 451 GRAS Notices voluntarily submitted to FDA from 1997 to 2012
- Analysis based on framework in Institute of Medicine's (IOM) 2009 Report on "Conflicts of Interest in Medical Research, Education and Practice"

IOM framework to analyze conflicts of interest

- COI = “Set of circumstances that creates a risk that the professional judgment or actions regarding a primary interest will be unduly influenced by a secondary interest.”
- Primary interest = Ensuring use is GRAS consistent with law
- Secondary interest = Potential for financial gain to additive manufacturer
- Does not evaluate specific decisions

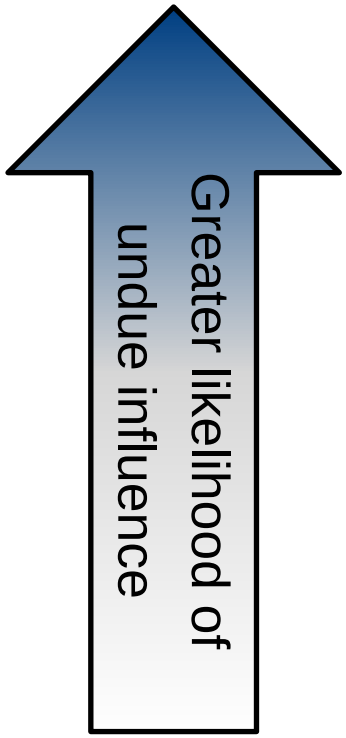
Assessing severity of COI: 2 part analysis

- Likelihood that a decision could be unduly influenced by COI
  - Value of secondary interest
  - Scope of relationship
  - Extent of discretion
- Seriousness of possible harm if the decision was influenced
  - Value of primary interest
  - Scope of the consequences
  - Extent of accountability

Likelihood that evaluation would be unduly influenced by the financial interests of an additive manufacturer*

Category of decision-maker

1. Employee of additive manufacturer
2. Employee of consulting firm selected by additive manufacturer
3. Expert panel selected by firm or manufacturer
4. Standing expert panel selected by third party
5. Employee of the FDA

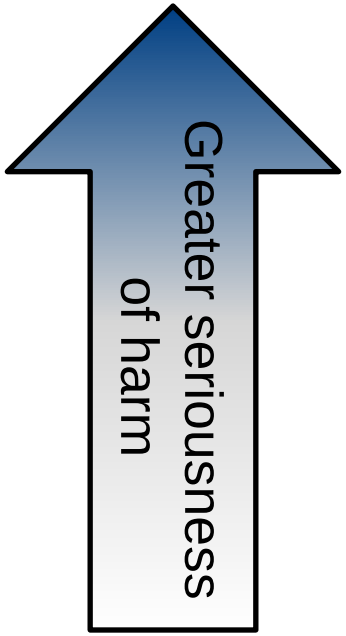


* Using Institute of Medicine 2009 framework

Seriousness of possible harm IF evaluation is unduly influenced by the financial interests of an additive manufacturer*

Type of FDA review

1. No review
2. FDA reviews but does not make notice publicly available
3. FDA reviews and makes notice publicly available



* Using Institute of Medicine 2009 framework

Results

- Types of individuals making determinations
- Frequency of experts serving on panels
- FDA actions when not notified

Type of individuals making GRAS evaluations submitted to FDA

Decision-maker	Number of notices
Employee of additive manufacturer	101 (22.4%)
Employee of consulting firm selected by additive manufacturer	60 (13.3%)
Expert panel selected by firm or manufacturer	290 (64.3%)
Standing expert panel selected by third party	0 (0%)

10 individuals served most frequently on the expert panels making GRAS evaluations

Individual	Number of expert panels served on
#1	128 (44.1%)
#2	41 (14.1%)
#3	40 (13.8%)
#4	38 (13.1%)
#5	35 (12.1%)
#6	34 (11.8%)
#7	34 (11.8%)
#8	28 (9.7%)
#9	28 (9.7%)
#10	27 (9.3%)

FDA actions when not notified

- Considered 1997 to 2012
- 1 action when FDA sought to obtain GRAS safety determination for which it had not been notified
  - Caffeine in alcohol beverages

Limitations

- Did not evaluate determinations:
  - Not voluntarily sent to FDA
  - Made by Flavor and Extract Manufacturers Association's (FEMA) Expert Panel
- Only considered employment of individuals
- Does not prove COI actually compromised GRAS determination process
  - Individual integrity
  - Organizational policies
  - No conflict between short-term gain and long-term brand

Due to insufficient information

Conclusions

- Financial conflicts of interest were ubiquitous in GRAS determinations by additive manufacturers
- Raises concern about:
  - Integrity of the process
  - Whether it ensures safety of the food supply
- Particular concern when manufacturer does not notify FDA
- FDA should:
  - Require it be notified of all GRAS determinations and of financial COIs
  - Make public all GRAS determinations including those by FEMA for flavors

For more information on Pew's Food Programs

Contact:

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EFSA's approach to independence and managing interests

Alberto Spagnolli
Head of Executive Office

Workshop on Potential Conflict of Interests in GRAS Additive Decisions - Washington DC, August 7 2013

EFSA's origins

Set up in 2002 in the wake of food scares (BSE, dioxins), with the objective to:

- underpin EU risk management through independent, high quality assessment of risks that is accepted across all EU Member States
- restore and maintain confidence in the EU food supply by consumers and trading partners

EU Food safety model

Risk Manager: EU Commission – Dir. Gen. Health and Consumers - Brussels

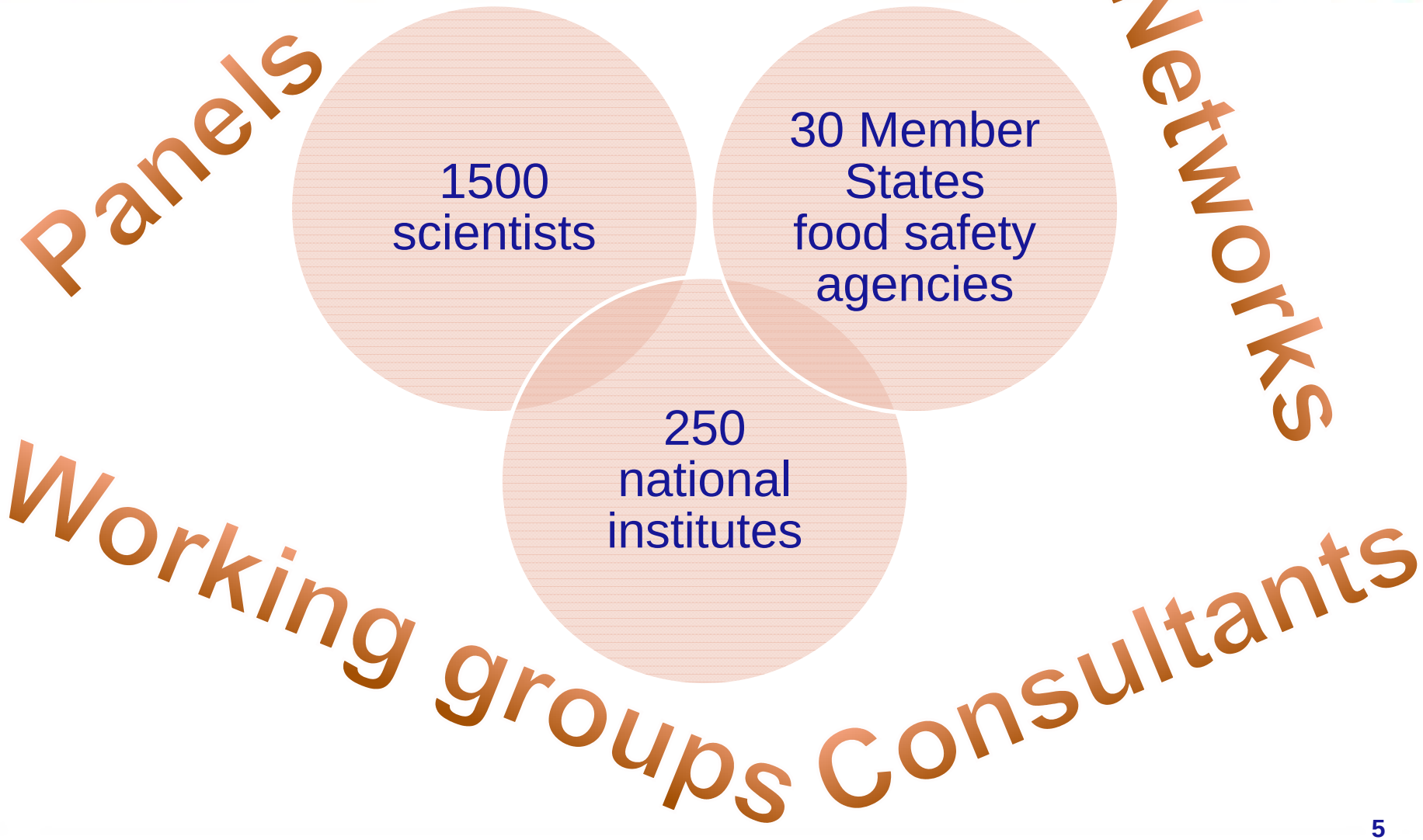
Risk Assessor: European Food Safety Authority - Parma

EFSA ‘s mission is to provide:

- ➢ independent scientific advice
- ➢ clear communication on risks.

EFSA: governance, actors and roles

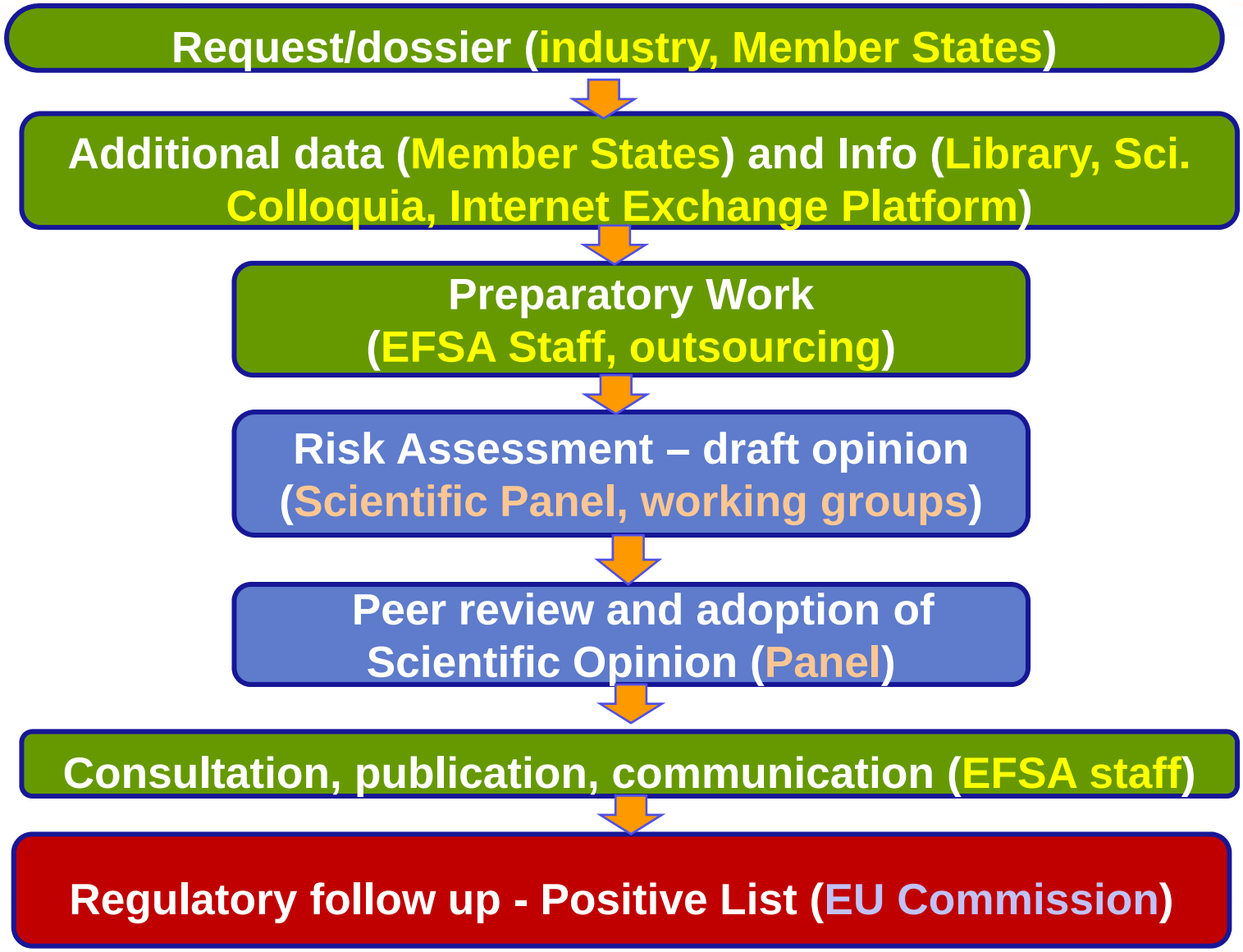
EFSA: mobilizing European scientists



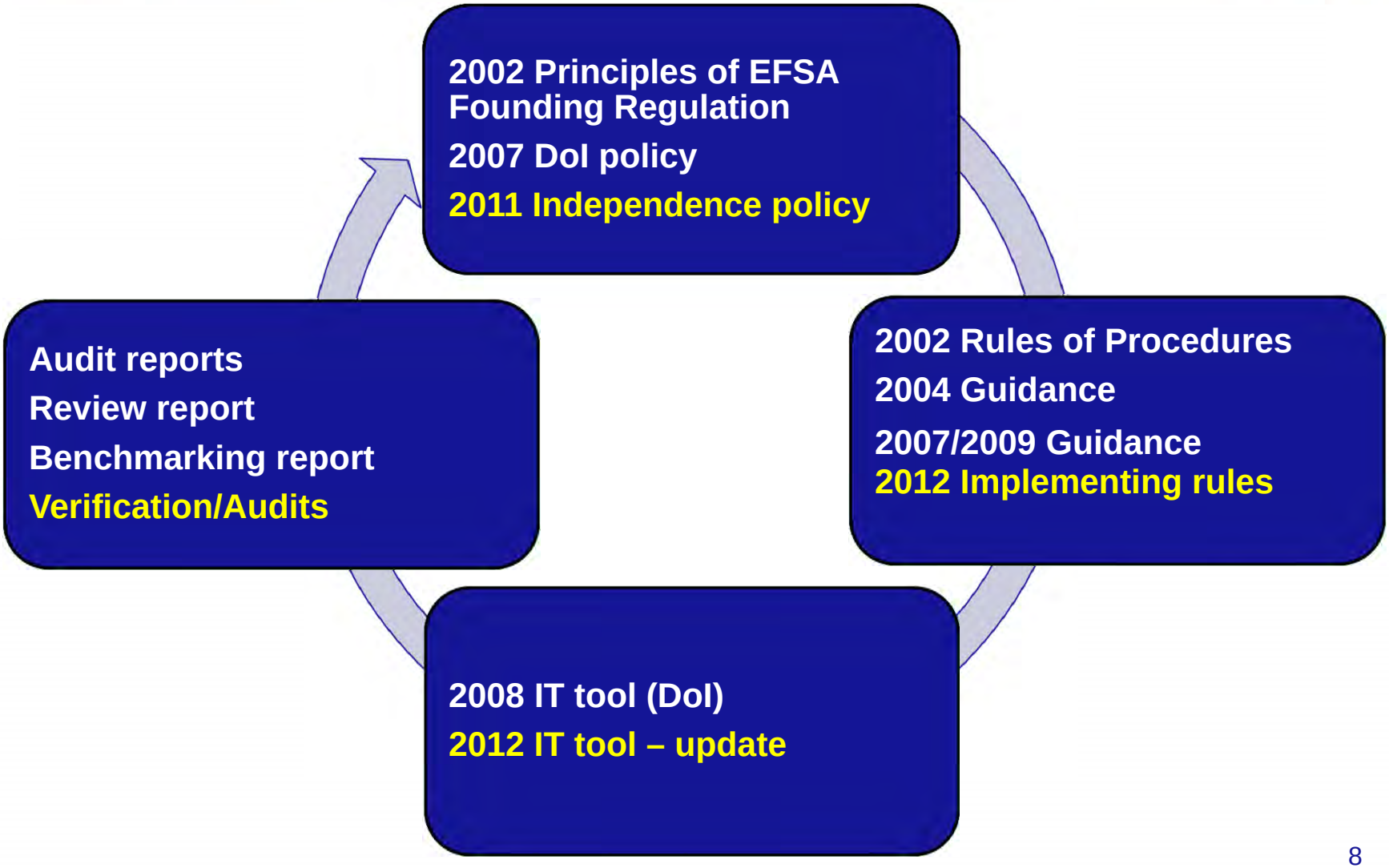
EU regulatory approach to food safety in the field of additives

- Only additives that are explicitly authorized by the EU regulator may be used – “Positive list”
- Prior to authorization, additives are evaluated by EFSA, based on dossiers submitted by industry or national authorities
- EU Commission decides on inclusion in the positive list based on EFSA’s evaluation
- No GRAS system available – marginal use of similar tools (QPS/TTC) for prioritisation purpose

EU workflow for risk assessment of additives



From DoI to Independence policy – continuous improvement



Independence policy: a wholistic approach

efsa
European Food Safety Authority

Organisational governance

- Role of Scientific Panels (the decision-makers) vs. EFSA staff.
- Management Board and Advisory Forum

Scientific governance and decision making

- Pluralism of contributions (panel, working group, EFSA staff, other experts)
- Panel deliberations (collegial decisions, recording of minority opinions)
- Quality assurance (guidance, SOP, compliance checks, ext.review)

Openness and Transparency

- Register of evaluations, expert names, Declarations of Interest
- Criteria for expert selection and for validation of data and studies, assessment methods
- Meetings agenda and minutes published, meetings open to observers
- Consultation (public or restricted) prior to adoption of scientific opinions

Managing interests – DoI policy

Independence policy

efsa
European Food Safety Authority

Collecting interests – Annual, Specific, Oral Declarations

efsa
European Food Safety Authority

Appointment process of members of Scientific Panels/Working groups (+annual renewal) ⟷ **Submission of ADoIs**

↓

Before each meeting takes place ⟷ **Submission of SDoIs**

↓

As a first point on the agenda of each meeting ⟷ **Submission of ODoI**

- **Responsibility of declaring rests with concerned individual**
- **DoIs cover a five year time span**

DoI - Interest Categories

I. Economic interests
II. Member of a Managing Body or equivalent structure
III. Member of a Scientific Advisory Body
IV. Employment
V. Ad hoc or occasional consultancy
VI. Research funding
VII. Intellectual property rights
VIII. Other membership or affiliation
IX. Other relevant interests
X. Interest of close family members

Screening interests – general approach

efsa
European Food Safety Authority

Interest declared, past/current

Mandate of the panel/WG etc.., single/multiple

Role of the expert (Chair, member, hearing expert)

Assessment of interests – key standards and principles I

- **Clear definition** of Conflict of Interest (re. OECD guidelines)
- **Consistent interpretation** in practice – checks and balances
- High level advisory body for difficult cases: **Committee on conflict of Interest**
- Transparency and clarity of **applied** criteria**: explanatory tables** laying down **prohibited and allowable interests** for each category
- Simple scheme of **preventive measures** (**in or out**)
- Full **process documentation** via DoI IT tool
- **Veracity checks** on a sample basis
- **Breach of trust** procedures

Assessment of interests – key standards and principles II

- **Stricter** approach for Panel/Woking Group **Chairmanship**
- **More inclusive scheme** for experts with interests in **Food Safety Organisations**

- **Horizontal exclusion criteria:**
  - **No expert** will be ever allowed **to review** or assess his or her **own work**
  - **No expert working with industry** on which EFSA outputs impact will be allowed on Scientific Panels and working groups

DOI – statistics and workload

Year	DOIs (ADOIs+SDOIs) Screened	Meeting agenda items scrutinised	Potential COIs prevented	Breach of trust procedures	Restrictions on members of other EFSA bodies
2011	8526	39,500	356	2	-
2012	6869	36,609	276	1	2

Potential conflict beween goals

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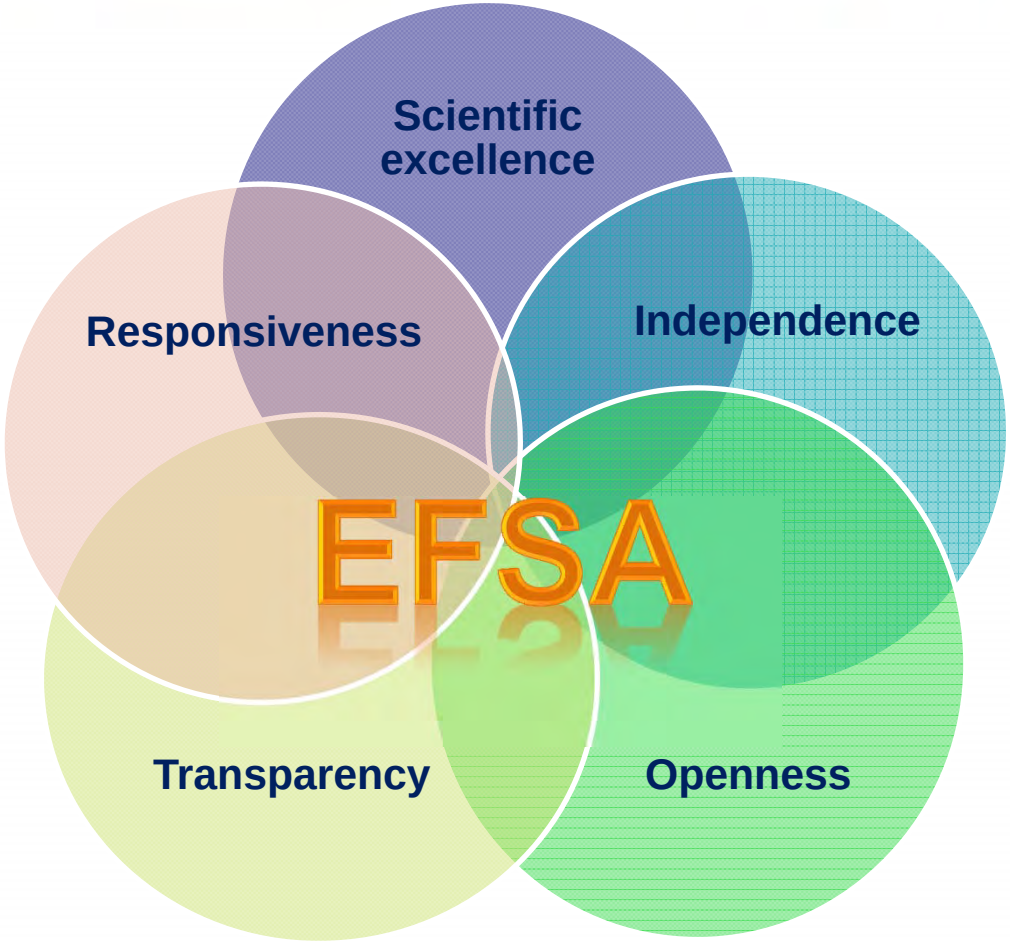


EFSA's guiding principles

Committed *since 2002*
to ensuring that Europe's food is safe

FDA Advisory Committees Conflict of Interest Review

The Pew Charitable Trusts Workshop
August 7, 2013

Jill Hartzler Warner, J.D.

Associate Commissioner for Special Medical Programs (acting)

Office of Special Medical Programs, FDA

Overview

- Definitions of conflict of interest
- Bases for COI policies
- Management of COI
- FDA focus
- FDA approach
- Challenges in application
- New initiatives

What is a conflict of interest?

- Bioethics definition/core principle
  - When professional judgment concerning a primary interest is unduly influenced by a secondary interest
- Federal standards of conduct
  - Focus: whether financial interests could be affected
- Other
  - Nonfinancial bias; perception of COI

Bases for COI policies

- Integrity of actions
- Maintain public trust and confidence in decisions
- Comply with statutory and regulatory requirements

Management of COI

- Identify relevant interests
- Review potential conflicts
- Limit certain relationships or holdings (recuse)
- Manage identified COI
- Publicly disclose certain relationships or holdings

FDA's Challenge and Goal

- Maintain public confidence in the advisory committee process ***and*** obtain the best expert advice
  - Robust COI policy
  - Enhanced efforts to identify non-conflicted experts

FDA Advisers are Special Government Employees

- Temporary service, not to exceed 130 days in a year
- Federal standards of conduct for government employees apply (some regulatory exemptions)

How are potential conflicts identified?

- SGEs submit a confidential financial disclosure statement that identifies potential conflicting financial interests
- FDA Form 3410 – assets, income, outside positions, consulting, grants, contracts, patents, speaking/writing.

Scope/Definition

- The law prohibits all employees (including SGEs) from participating in any **particular Government matter** that will have a **direct and predictable effect** on their **financial interests.**
- It also prohibits employees from acting in Government matters that will affect the financial interests of others with whom they have certain relationships (imputed interests).

18 U.S.C. 208

Whose interests?

- SGE
- Spouse
- Minor child
- General partner
- Organization in which SGE serves as officer, director, trustee or employee
- Prospective employer

Which interests?

- Stocks and investments
- Primary employment
- Consulting or advising
- Grants, contracts
- Patents/royalties/trademarks
- Serving as expert witness
- Speaking/writing

Exceptions for SGEs

- SGEs can participate in **matters of general applicability** where the interest that creates the conflict arises from the SGE's non-federal employment
  - as long as the matter does not impact the employer or employee other than as part of a class

Exemptions

- Diversified mutual funds
- Publicly traded securities – matter involving specific parties
  - <$15K sponsor
  - <$25K competitors of sponsor
- Publicly traded securities – matter of general applicability
  - <$25K one company, <$50K aggregate

If a conflict is identified

- Sell / Divest
- Recusal / Disqualification
- Waiver
  - May be granted if the need for service outweighs potential for a conflict of interest
  - Public disclosure: all waivers posted to FDA's website (21U.S.C. 379d-1)

Challenges in application

- Administratively complex
  - Because focus is whether the AC meeting discussion and outcomes will affect the financial interest, reporting and analysis is individual and meeting-specific
- Does the process deter some SGEs?
  - Detailed reporting of broad scope of interests
  - Scrutiny by media and stakeholders

Challenges (cont.)

- Focus is on **current financial** interests
  - Some stakeholders have concerns about past financial interests
  - Nonfinancial bias may also be a concern, but difficult to quantify.
- Public disclosure of waivers is an FDA-specific requirement
- High public and media interest
- Attract and retain the top experts

What's next?

- Revising guidance documents to reflect FDASIA amendments
- New guidance on "appearance" issues
  - 5 CFR 2635.502
- Developing partnerships to leverage expert recruitment efforts
- Institute of Medicine project to develop harmonized COI reporting

For Further Information

- www.fda.gov/AdvisoryCommittees/default.htm

- Advisory Committee Oversight and Management Staff/OSMP

  301-796-8220

Conflicts of Interest and Subconscious Bias

Sunita Sah

Assistant Professor of Business Ethics, Georgetown University

Research Fellow, Edmond J. Safra Center for Ethics, Harvard University

Many different types of Conflicts of Interest (COIs)

- Clash between professional responsibilities and personal (often material) interests
- Clash between two professional interests

The presence of a COI does not mean that someone has succumbed to the COI by giving biased advice

Why are COIs important?

- Steer professionals away from primary professional goal
- Can lead to increased costs

Why do physician's accept?

Virtually all (94%) physicians have some type of relationship with industry (Campbell et al. 2007)

- Influence over clinical practice guidelines
  (Kassirer 2004)
- Biases from industry support of clinical trials,
  (Smith 2005, Rochon et al 1994, Bekelman et al. 2003, Bero et al. 2007, Lexchin et al. 2003)

Subconscious and unintentional bias

Being biased by a COI is traditionally (but often incorrectly) thought to stem from intentional corruption rather than unintentional bias

Psychological mechanisms involved in accepting (and succumbing to) potential conflicts of interest.

Why do professionals accept and succumb to COIs?

- Feeling deprived / entitled
- Sense of invulnerability

Because I'm Worth It

- 80.3% believed they were entitled to gifts from industry due to hardships, described as "considerable debt and minimal income"

(Sierles et al., 2005)

- Adams' 'equity theory' postulates that individuals who feel underpaid are likely to respond by lowering their input (i.e. their work contributions) or by attempting to raise their rewards

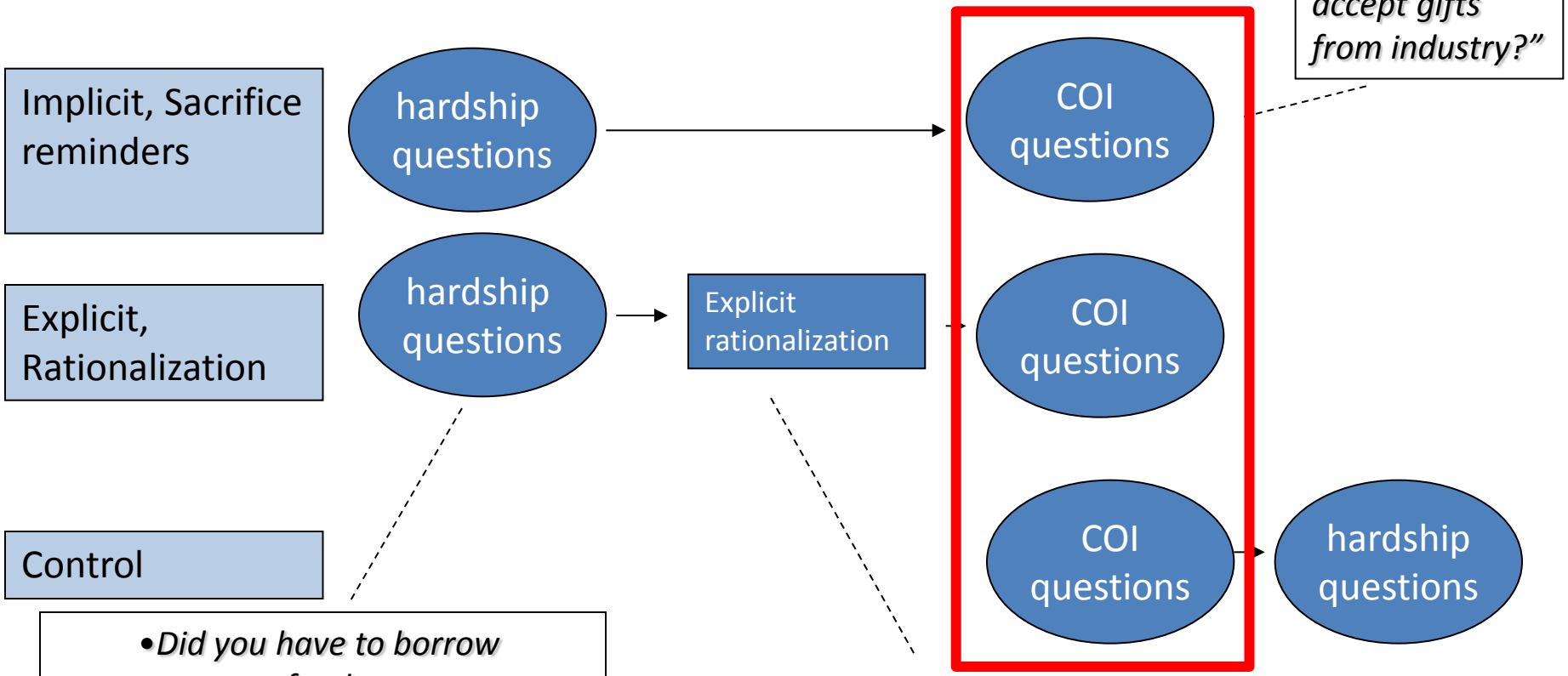
(Adams, 1965)

Method: 301 U.S. young physicians, 90 from a population of 100 residents at U. of Pittsburgh Children's Hospital, randomly assigned to 3 conditions.

Sah, S. and Loewenstein, G. (2010). Effect of Reminders of Personal Sacrifice and Suggested Rationalizations on Residents' Self-reported Willingness to Accept Gifts: A Randomized Trial . *JAMA*. *304*(11),1204-1211.

Method: 301 U.S. young physicians, 90 from a population of 100 residents at U. of Pittsburgh Children's Hospital, randomly assigned to 3 conditions.

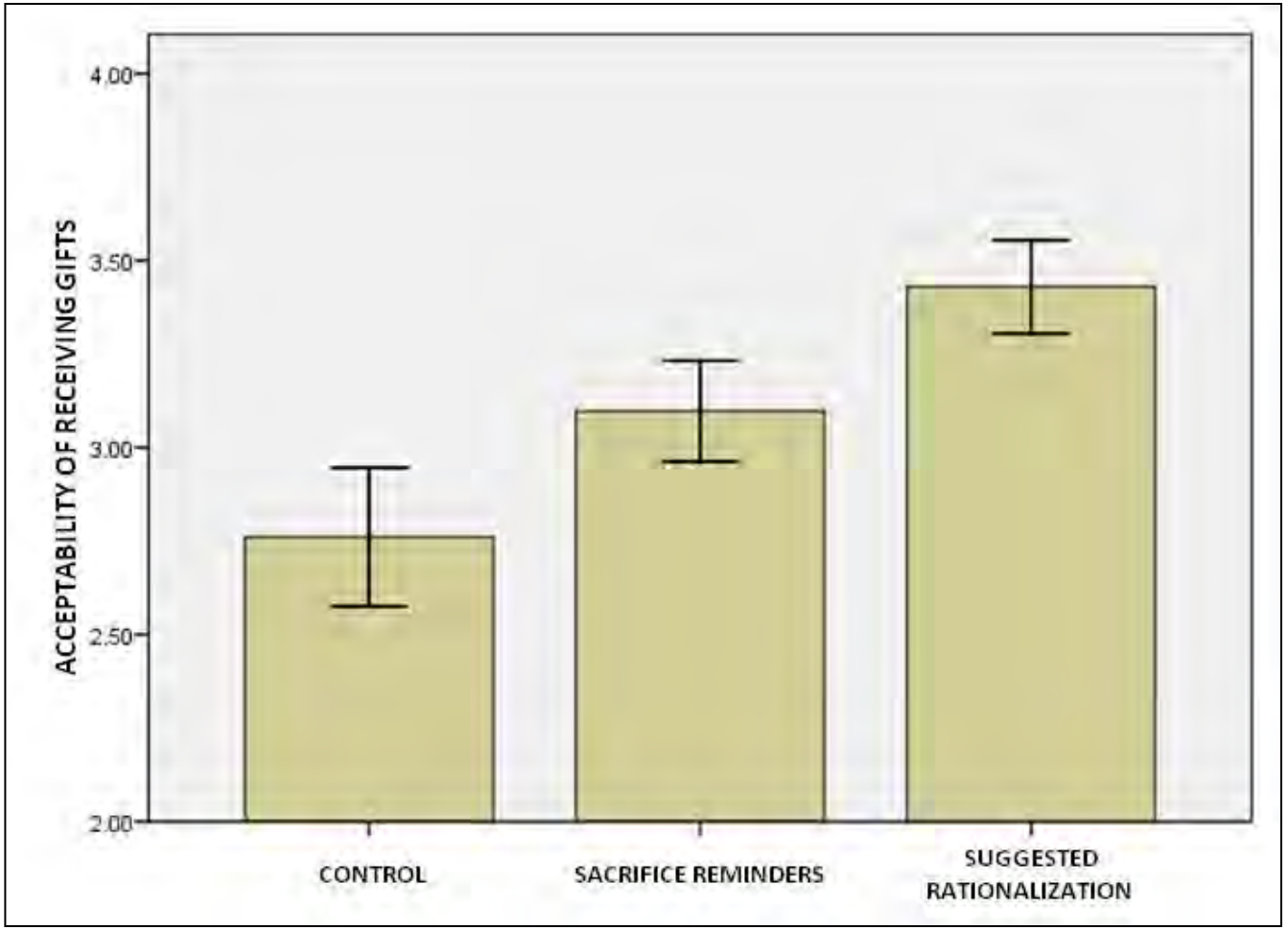
e.g., "Do you think it is okay for a doctor to accept gifts from industry?"



- *Did you have to borrow money to fund your education?*
- *Please indicate your average gross annual salary?*
- *How many hours of sleep do you get on average per night when (not) on call?*

"Some physicians believe that the stagnant salaries and rising debt levels prevalent in the medical profession justifies accepting gifts and other forms of compensation and incentives from the pharmaceutical industry. To what extent do you agree or disagree that this is a good justification."

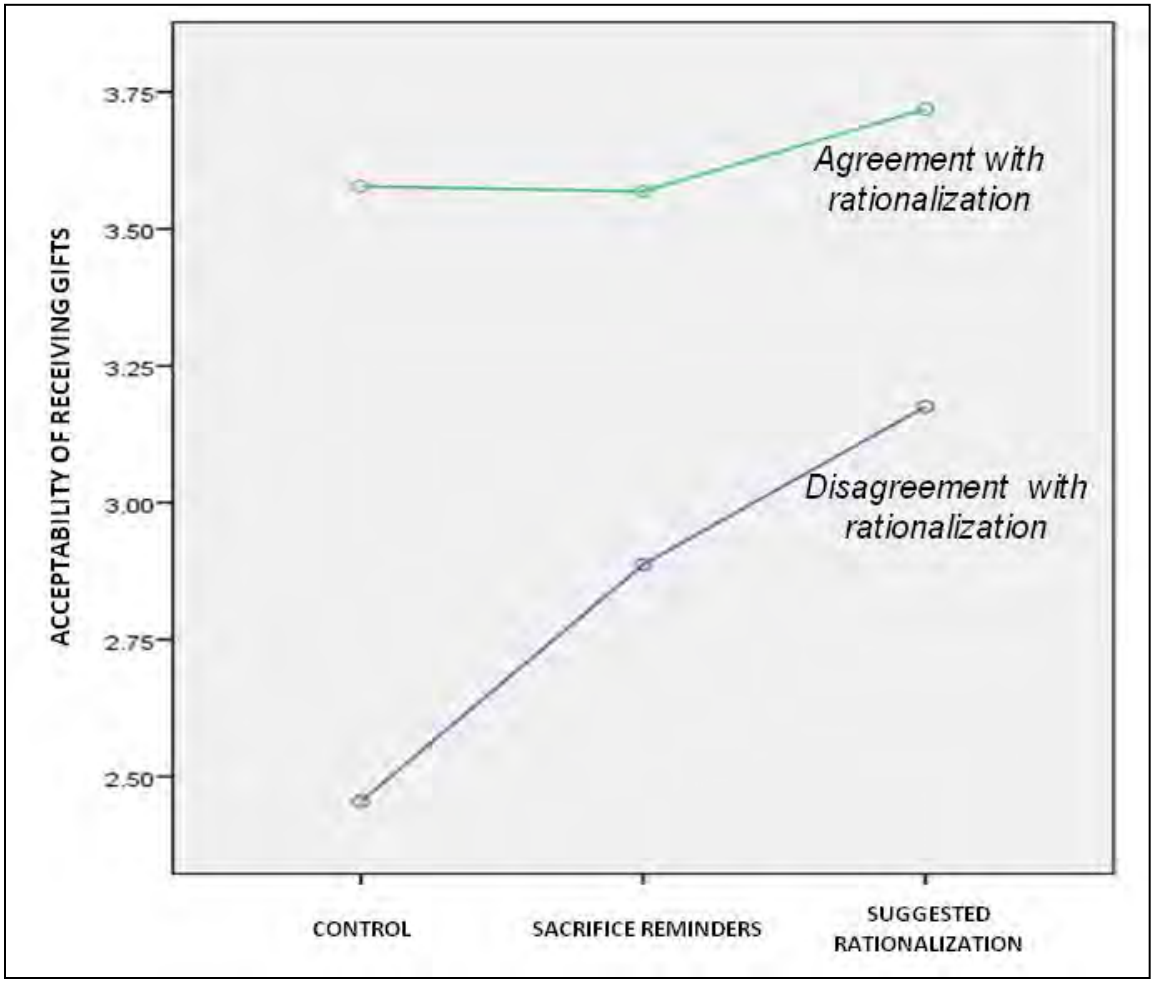
Sacrifice primes increases COI acceptability



Significant effect of sacrifice-reminders on acceptability of receiving gifts (from 21.7% to 47.5%).

The suggested rationalization further increased gift acceptability (to 60.3%).

Acceptability of receiving gifts by condition and agreement with rationalization



Those who agreed with the rationalization are more likely to accept gifts.

Those who *disagreed* with the rationalization are more vulnerable to changing their view on accepting gifts with sacrifice-reminders and suggested-rationalization primes.

An additional manipulation..

- Sacrifice reminders and Rationalization groups further randomly assigned to “feel-rich” and “feel-poor” subgroups

  E.g., for the feel-poor subgroups, the lowest category for salary is $0 to $100,000 and the highest category is $350,000 or higher vs. $0 to $20,000 and $50,000 for the feel-rich subgroups

feel poor…

feel rich…

Feel-rich feel-poor results

- Poor working conditions were reported by 50.0% of those in the feel-poor subgroups compared with 37.3% in the feel rich subgroups ($\chi 2$ = 4.97; *P*= .03).

- COI acceptability was greater in the feel-poor subgroups (60.9%) than in the feel-rich subgroups (47.6%), (*P* = .04)

Summary

- Implicit reminders and suggested rationalizations increase willingness to accept COIs
- Poor working conditions (subjective perception) increase willingness to accept COIs
- “Objective” perceptions turn out to subjective and influenced by irrelevant factors
- May occur on a subconscious level

The role of RATIONALIZATIONS in deciding whether COIs are acceptable

Sense of invulnerability

- Physicians say they are not influenced by industry gifts (although they admit that other physicians are likely to be influenced)

(McKinney et al 1990)

Participants take a multi-component study

- Part 1: various scenarios / questions on how likely they are to be influenced by small gifts:
  - 84% say unlikely to be influenced

- Part 2: $10 allocation task
  - Participant receives $5 (from Alex*)
  - Participant observes someone else receiving $5 (from Alex*)

- Part 3: Judge
  - Evaluate the work (solutions for common world issues) of 2 people

* "Alex" was one of several gender neutral names used for the 'proposer'

Judge work of Person 1 (Alex* or unknown) and Person 2 (always unknown)

Received $5 Alex* Evaluate Alex vs. P2	Observed Alex $5 Evaluate Alex vs. P2
Received $5 Alex Evaluate unknown vs. P2	Observed Alex $5 Evaluate unknown vs. P2

* "Alex" was one of several gender neutral names used for the 'proposer'

Results

- If they received $5 from Alex*, judges evaluate Alex's solutions higher than in the three other conditions (p = .02).
- Deny that the $5 influenced them
- Effect remains even when incentivized to give answers that match an independent judge

* "Alex" was one of several gender neutral names used for the 'proposer'

Manager Study

- 617 managers completed questions on "professionalism"
  - Professionals are able to self-regulate how influenced they become when accepting gifts
  - Accepting gifts does not compromise my integrity
  - Professionals who are influenced by gifts lack integrity
  - I won't allow my opinion to be swayed even if I receive a gift

- Read series of scenarios regarding a gift / bribe and asked if they would accept and would they be influenced by the gift

Results

- The higher the level of "professionalism," the *more* likely they were to accept the gift and the *less* likely they were to admit to being influenced by the gift
  - Sig. positive correlation between professionalism and accepting gifts
  - Sig. negative correlation between professionalism and willing to admit that they could be influenced by gifts

Manager Behavioral Study

- Approx. 350 managers: Write about:
  - High integrity at work
  - Last trip to grocery store or no writing task
- Professionalism scale
  - High integrity lead to high professionalism rating
- Received $5 (from Alex*)
- Judge work of Person 1 (Alex* or unknown) and Person 2 (always unknown)

Judge work of Person 1 (Alex* or unknown) and Person 2 (always unknown)

High Professionalism
Evaluate Alex* vs. P2

Low Professionalism
Evaluate Alex * vs. P2

High Professionalism
Evaluate unknown vs. P2

Low Professionalism
Evaluate unknown vs. P2

* "Alex" was one of several gender neutral names used for the 'proposer'

Results

- Significant bias towards Alex shown when
  1. High professionalism
  2. Received $5 from Alex

- Deny that the $5 influenced them
- Effect remains even when incentivized to give answers that match an independent judge

Summary

- High professionalism may make people more vulnerable to
  - View COIs as acceptable
  - Succumb to bias from COIs

- Remain unaware of the bias

1. Cannot predict the bias in advance
2. Cannot recognize the bias in hindsight

Conclusion

Rationalization plays an important role in much conflict-of interest related behavior -- e.g., physicians can persuade themselves that:

- drugs they are getting paid to prescribe, or giving paid talks to promote, really *are* the best
- patients they are referring to clinical trials really *will* benefit from it
- they really *did* deserve authorship credit for that academic paper, despite having not been involved in the research

Sah, S. (2012). Conflicts of Interest and Your Physician: Psychological Processes that Cause Unexpected Changes in Behavior. *Journal of Law, Medicine and Ethics, 40*(3), 482-487.

Industry Rationalizations

Pharmaceutical employees can persuade themselves that:

- drugs they are promoting or getting incentivized to sell really *are* the best
- Influencing physician prescribing with gifts is acceptable because
  - all companies do this
  - our drugs really *are* the best
- Off label marketing or using key opinion leaders to influence prescribing is acceptable because our drugs really *are* the best
- Focusing on maximizing profits enables us to put more money into research and development

Objective decisions are often subjective

Role of self-serving biases and rationalizations

Disclosure

- Perverse effects
  - Advisors → increased bias (moral licensing, strategic exaggeration)
  - Advice Recipients → increased pressure to take advice (Sah et al, 2013)
- Work well
  - External disclosure – arms length, time to reflect (Sah et al, 2013)
  - Encourages advisors to reject the COI (Sah & Loewenstein, 2013)

General Conclusions

- Problem of COIs is not one of deliberate corruption, but of subconscious bias
- More work needs to be done to determine when disclosure works well and when it can backfire
- The only effective way to mitigate the problems associated with COIs is to realign incentives to eliminate conflicts

Thank you!

Research Papers

- Sah, S. and Loewenstein, G. (2010). Effect of Reminders of Personal Sacrifice and Suggested Rationalizations on Residents' Self-reported Willingness to Accept Gifts: A Randomized Trial . *JAMA*. 304(11),1204-1211.

- Sah, S. (2012). Conflicts of Interest and Your Physician: Psychological Processes that Cause Unexpected Changes in Behavior. *Journal of Law, Medicine and Ethics*, 40(3), 482-487.

- Sah, S., & Larrick, R. (2013). I am Immune: A Sense of Invulnerably Predicts Increased Acceptance of, and Influence from, Conflicts of Interest. *Research in Progress.*

- Sah, S., & Loewenstein, G. (2013). Nothing to Declare: Mandatory and Voluntary Disclosure Leads Advisors to Avoid Conflicts of Interest. *Under Review.*

- Sah, S., Loewenstein, G., & Cain, D. (2013). The Burden of Disclosure: Increased Compliance with Distrusted Advice. *Journal of Personality and Social Psychology. 104*(2), 289-304.

Available at www.sunitasah.com/research

Why Conflicts of Interest Matters

Sheldon Krimsky
Tufts University
Brooklyn College, CUNY
www.tufts.edu/~skrimsky

Workshop on Potential Conflict of Interest in GRAS Additive Decisions

Pew Charitable Trusts

Washington, D.C.

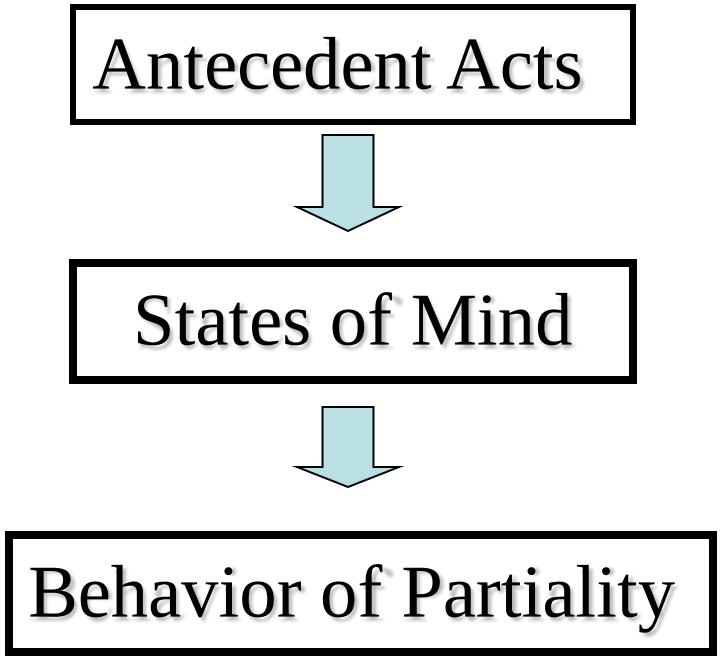
August 7, 2013

Preventing COI in Public Life

"Because we cannot prevent officials from mentally taking notice of their own interests, we prohibit the act of holding certain kinds of interests in the first place"

A. Stark *Conflicts of Interest in American Public Life,* 2000.

Anatomy of Conflict of Interest



- ***Antecedent Acts*:** The factors that condition the state of mind of an individual toward partiality
- ***States of Mind***: The affected sentiments, proclivities and affinities conditioned by the antecedent acts.
- ***Behavior of Partiality***: The outcome behavior that is affected by the antecedent acts and states of mind.

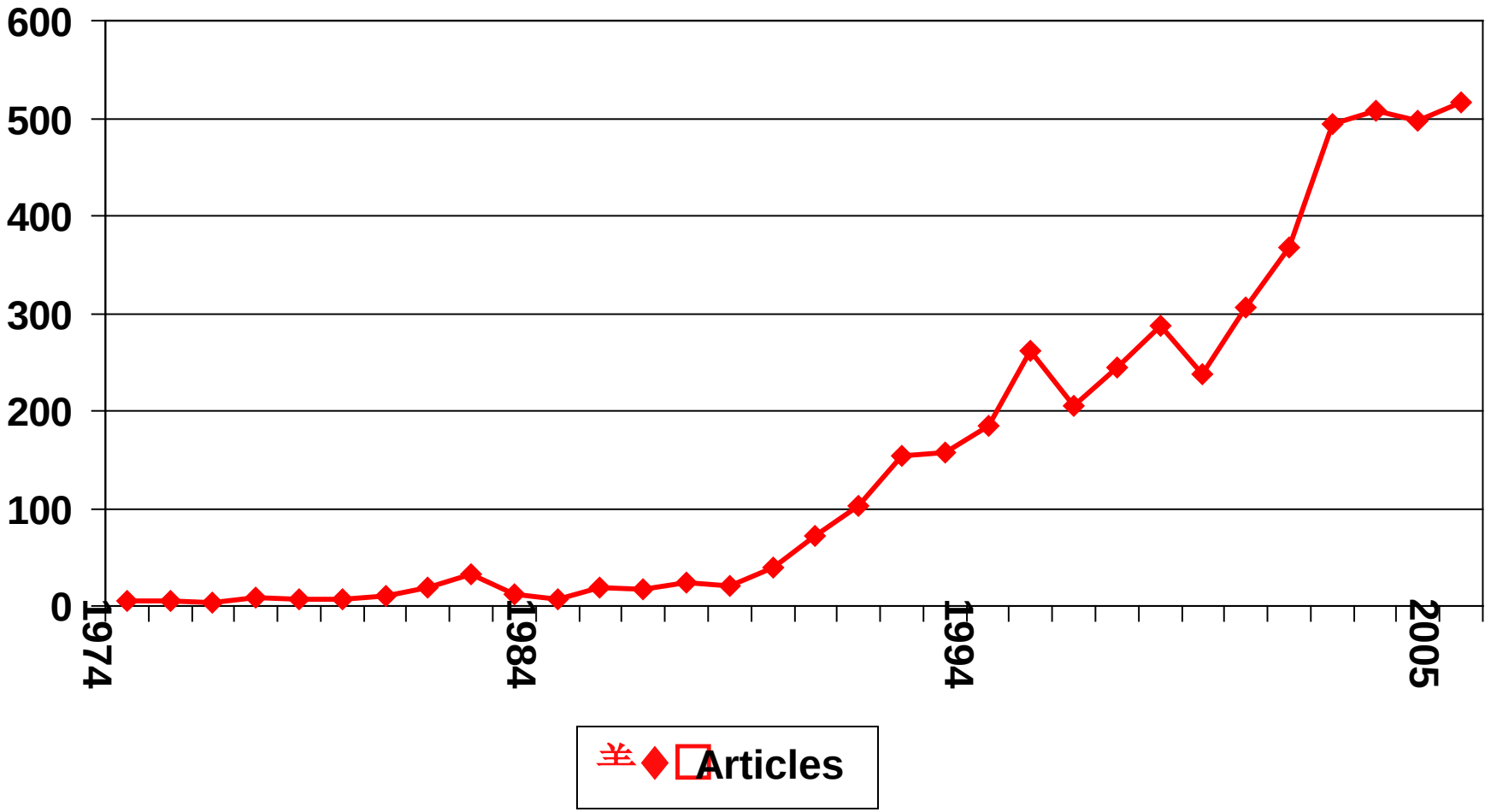
Before 1980 we never heard the words ***scientist*** and ***conflict of interest*** mentioned in the same breath.

Today, leading science journals are struggling with their integrity in the face of public skepticism over their credibility?

Leaders in the medical field are claiming that conflicts of interest have created a crisis in clinical medicine?

Federal agencies have been more attentive to transparency of financial conflicts of interest.

Articles on Conflict of Interest Cited Annually in MEDLINE, 1974 – 2005



Ethical Foundations of Conflict of Interest

There are four ethical grounds for managing or proscribing conflicts of interest among university faculty or within government. They can be characterized by the terms.

- Stewardship
- Transparency,
- Consequentialism, and
- Integrity of science.

- Stewardship pertains to the responsibility for the proper management of public funds and resources used in carrying out research.

- Transparency requires that the methods, sources of materials, background literature, contributions of authors to the research project, and limitations to the study are made available to the reviewers, journal editors, and readers.

Consequentialism refers to the link between a behavior (such as a COI) and the quality of the research outcome (such as bias).

Finally,

Integrity of Science speaks to the public confidence in the scientific enterprise, which could be compromised by conflicts of interest despite complete transparency and an outcome of objective science.

Conflict of Interest and Scientific Journals

Can you believe what you read?

Scientists financial interests can bias the papers and review articles that they write, studies suggests. But what can editors do to police the issues? Frank van Kolfschooten examines journal's policies oon conflicts of interest.

Survey of Scientists' Misbehavior

In a survey of several thousand early and mid-career scientists in the United States funded by the National Institutes of Health, scientists were asked to report on their own behaviors.

When asked whether they ever change the design, methodology or results of a study in response to pressure from a funding source: 20.5% mid-career scientists and 9.5% early-career scientists answered affirmatively.

B.C. Martinson, M.S. Anderson, and R. de Vries. Scientists behaving badly. *Nature* 435:737-738 (June 9, 2005).

Does the Source of funding affect the outcome of research?

"Evidence suggests that financial ties that intertwine industry, investigators, and academic institutions can influence the research process. Strong and consistent evidence shows that industry-sponsored research tends to draw pro-industry conclusions." (p. 463).

Bekelman et al. Scope and Impact of Financial Conflicts of Interest in Biomedical Research *JAMA* 289:455 (2003)

Scope and Impact of Financial Conflicts of Interest in Biomedical Research

A Systematic Review

Justin E. Bekelman, AB
Yan Li, MPhil
Cary P. Gross, MD

Context Despite increasing awareness about the potential impact of financial conflicts of interest on biomedical research, no comprehensive synthesis of the body of evidence relating to financial conflicts of interest has been performed.

Objective To review original, quantitative studies on the extent, impact, and management of financial conflicts of interest in biomedical research.

Data Sources Studies were identified by searching MEDLINE (January 1980-October 2002), the Web of Science citation database, references of articles, letters, commentaries, editorials, and books and by contacting experts.

Study Selection All English-language studies containing original, quantitative data on financial relationships among industry, scientific investigators, and academic institutions were included. A total of 1664 citations were screened, 144 potentially eligible full articles were retrieved, and 37 studies met our inclusion criteria.

Data Extraction One investigator (J.E.B.) extracted data from each of the 37 studies. The main outcomes were the prevalence of specific types of industry relationships, the relation between industry sponsorship and study outcome or investigator behavior, and the process for disclosure, review, and management of financial conflicts of interest.

Data Synthesis Approximately one fourth of investigators have industry affiliations, and roughly two thirds of academic institutions hold equity in start-ups that sponsor research performed at the same institutions. Eight articles, which together evaluated 1140 original studies, assessed the relation between industry sponsorship and outcome in original research. Aggregating the results of these articles showed a statistically significant association between industry sponsorship and pro-industry conclusions (pooled Mantel-Haenszel odds ratio, 3.60; 95% confidence interval, 2.63-4.91). Industry sponsorship was also associated with restrictions on publication and data sharing. The approach to managing financial conflicts varied substantially across academic institutions and peer-reviewed journals.

Conclusions Financial relationships among industry, scientific investigators, and academic institutions are widespread. Conflicts of interest arising from these ties can influence biomedical research in important ways.

JAMA. 2003;289:454-465 www.jama.com

INDUSTRY SUPPORT OF BIOMEDICAL research in the United States increased dramatically in the last 2 decades. Industry's share of total investment in biomedical research and development grew from approximately 32% in 1980 to 62% in 2000, while the federal government's share fell.[1,2] During this period, the relationship between academic institutions and industry flourished, spawning medical advances, creating new biotechnology markets, and providing needed support for further discovery. However, an entanglement of relationships among industry, investigators, and academic institutions also emerged.

Conflicts of interest are "a set of conditions in which professional judgment concerning a primary interest (such as a patient's welfare or the validity of research) tends to be unduly influenced by a secondary interest (such as financial gain)."[3] Financial interests are not the only, or necessarily the most powerful, secondary interests faced by investigators and academic institutions. For investigators, other pressures, including the desire for professional recognition and the need to compete successfully for research funding, are intrinsic to the research process.[4] Institutions also confront myriad pressures arising from balancing the needs of diverse departments and constituencies. However, financial interests related to biomedical research are nonobligatory and often unrecognized unless disclosed. They are the focus of current national discussion because they induce public anxiety about the influence of money on the research process.[3,5,6]

Author Affiliations: Department of Medicine (Mr Bekelman and Dr Gross) and Department of Biostatistics (Ms Li), Yale University School of Medicine, New Haven, Conn.

Financial Disclosures: Dr Gross has served as a consultant and scientific advisory board member to AstraZeneca. Mr Bekelman has served as a consultant to Turbogenomics Inc.

Corresponding Author and Reprints: Cary P. Gross, MD, Primary Care Center, Yale University School of Medicine, 333 Cedar St, PO Box 208025, New Haven, CT 06520 (e-mail: cary.gross@yale.edu).

Does conflict of interest matter?

- 11 studies compared the outcome of studies sponsored by industry and those not so sponsored
- In every study those that were sponsored were more likely to have a finding favourable to industry
- When the results were pooled the sponsored studies were almost four times more likely to find results favourable to industry

- Bekelman JE, Li Y, Gross CP. Scope and impact of financial conflicts of interest in biomedical research. A systematic review. JAMA 2003; 289: 454-65.

A financial interest does not have to be great for the influence to be undue. Indeed, social science research suggests that gifts of small value may influence decisions. It also suggests that influence may operate without an individual being conscious of it. When a secondary interest has inappropriate weight in a decision and distorts the pursuit of a primary interest, it is exerting undue influence. (from DHHS rule on COI)

Individuals accused of having a conflict of interest often say that they would never let financial interests influence their decisions. This objection to conflict of interest policies misses the point. Because the conflict is a set of circumstances or conditions involving a risk rather than a specific individual decision, the existence of a conflict of interest does not imply that any individual is improperly motivated. Nevertheless, an individual professional might still object that it is not fair to generalize in this way. He or she may want to say: “Look at my actual decisions and consider my distinguished reputation.” However, conflict of interest policies are by their nature designed to avoid the need to investigate individual cases in this way. For at least two reasons, such policies do not focus on the motives in a particular case.

May 30, 2006
Editorial

Industry's Role in Hypertension

If the American Society for Hypertension hoped to devise an expanded definition of the condition that would be scientifically and ethically defensible, it sure picked the wrong way to do it. Virtually every key step in its efforts to redefine hypertension from mere high blood pressure to a broader syndrome has been financed by pharmaceutical companies that would gain by selling drugs to more people.

As described by Stephanie Saul in The Times on May 20, Merck, Novartis and Sankyo gave the small medical society $75,000 in unrestricted grants that were used to develop a new definition, and $700,000 more in unrestricted grants that financed dinner lectures to promote the new definition. The drug companies have too much self-interest to be allowed even a peripheral role in defining illness.

Comparison of "B" Readers' Interpretations of Chest Radiographs for Asbestos Related Changes[1]

Joseph N. Gitlin, DPH, Leroy L. Cook, BA, Otha W. Linton, MSJ, Elizabeth Garrett-Mayer, PhD

Rationale and Objectives. The purpose of this study was to determine if chest radiographic interpretations by physicians retained by attorneys representing persons alleging respiratory changes from occupational exposure to asbestos would be confirmed by independent consultant readers.

Materials and Methods. For 551 chest radiographs read as positive for lung changes by initial "B" readers retained by plaintiffs' attorneys, 492 matching interpretative reports were made available to the authors. Six consultants in chest radiology, also B readers, agreed to reinterpret the radiographs independently without knowledge of their provenance. The film source, patient name, and other identifiers on each film were masked. The International Labor Office 1980 Classification of Chest Radiographs (ILO 80) was used with forms designed by the US National Institute of Occupational Safety and Health to record the consultants' findings. The results were compared with initial readings for film quality, complete negativity, parenchymal abnormalities, small opacities profusion, and pleural abnormalities using chi-square tests and kappa statistics.

Results. Initial readers interpreted study radiographs as positive for parenchymal abnormalities (ILO small opacity profusion category of 1/0 or higher) in 95.9% of 492 cases. Six consultants classified the films as 1/0 or higher in 4.5% of 2,952 readings. Statistical tests of these and other comparable data from the study showed highly significant differences between the interpretations of the initial readers and the findings of the consultants.

Conclusion. The magnitude of the differences between the interpretations by initial readers and the six consultants is too great to be attributed to interobserver variability. There is no support in the literature on x-ray studies of workers exposed to asbestos and other mineral dusts for the high level of positive findings recorded by the initial readers in this report.

Key Words. Asbestosis; chest x-ray interpretation; ILO classification; disability compensation.

In 2000, the authors were requested by attorneys active in asbestos compensation litigation to develop an acceptable method of obtaining reliable interpretations of chest radiographs. The methods and results of a multiple reader trial conducted in response to their request are presented in this report. The study design was a comparison of six independent readings of chest radiographs by qualified consultant "B" readers with single readings of the same radiographs by one of several initial B readers selected by plaintiffs' counsel.

Chest radiographs have been used in public health programs for detection of tuberculosis and for legally mandated examinations of coal miners and other workers exposed to mineral dusts, including asbestos. Under current federal regulations, coal miners, uranium miners and millers, and workers with asbestos or asbestos-containing products who claim occupationally related respiratory disease or disability must support their claims with a posteroanterior (PA) chest radiograph. The findings of these

Acad Radiol 2004; 11:843–856

[1] From the Department of Radiology, Johns Hopkins Medical Institutions, 14208 Northwyn Drive, Silver Spring, MD 20904, PennyPoor Consultants, Shenandoah Junction, WV, International Society of Radiology, Bethesda, MD, Department of Oncology, Division of Biostatistics, Johns Hopkins School of Medicine, Baltimore, MD. Received June 10, 2003; revision received November 5, 2003; revision received February 2, 2004; revision received February 23, 2004; revision received March 8, 2004; revision received March 22, 2004; revision accepted April 12, 2004. **Address correspondence to** J.N.G. e-mail: jgitlin@jhmi.edu

doi:10.1016/j.acra.2004.04.012

INTERPRETATION OF CHEST X-RAYS

492 abnormal chest X-rays, according to 30 plaintiff-hired “B” readers (hirees).

Films re-read by 6 blinded “B” readers (independents).

(“B” readers are certified by NIOSH; all used standard DHSS form OMB No. 0920-0020)

Gitlin et al Acad. Radiol 2004;11:843-856

RESULTS (%)

	hirees	independents
Parench. abn.	96	5
Pneumocon.	97	6
Pleural abn	26	8
Film normal	0	38

FDA is criticized for hinting it may loosen conflict of interest rules

by Jeanne Lenzer

The US Food and Drug Administration has come under fire for suggesting that it may loosen conflict of interest rules for its advisers, because of a shortage of experts without ties to the drug and medical devices industry.

The FDA's commissioner, Margaret Hamburg, said that strict rules on conflict of interest implemented in 2008, which limit the proportion of advisory panellists with industry ties to 13%, may be slowing down approvals of products and hindering innovation.

Because the conflicts of interest held by scientists in the subject matter of their research are potential biasing factors, conflicts of interest should be as transparent as any other aspect of research. Scientists may have potentially biasing intellectual interests, such as a predilection for a certain theory or an association with certain advocacy groups. These interests are usually expressed by the authors' own writings or public activities. Financial COIs, however, have been traditionally more secretive, and therefore their biasing effects are less transparent.

From: Combatting the Funding Effect in Science, *Stanford Law & Policy Review*, 2010.

Senator Chuck Grassley led a right to know campaign on conflicts of interest

- Senator Grassley wrote on his website:
- "We rely on the advice of doctors, and leading researchers influence the practice of medicine…Taxpayers spend billions each year on prescription drugs and devices through Medicare and Medicaid. The National Institutes of Health distributes $24 billion annually in federal research grants. So the public has a right to know about financial relationships between doctors and drug companies."

Various reviews have found extensive selective reporting in study publications

(McGauran *et al. Trials* 2010, **11**:37)

- For example, an analysis of 192 randomized drug trials in various indications showed that only 46% of publications stated the frequency of specific reasons for treatment discontinuation due to toxicity . Outcomes are not only selectively reported, but negative results are reported in a positive manner and conclusions are often not supported by results data.

A comparison of study characteristics reported in FDA reviews of New Drug Applications (NDAs) with those reported in publications found that 9 of 99 conclusions had been changed in the publications, all in favor of the new drug.

Effect of Interpretive Bias on Research Evidence

Ted J. Kaptchuk BMJ 2003

- Facts do not accumulate on the blank slates of researchers' minds and data simply do not speak for themselves.[1] Good science inevitably embodies a tension between the empiricism of concrete data and the rationalism of deeply held convictions. Unbiased interpretation of data is as important as performing rigorous experiments. This evaluative process is never totally objective or completely independent of scientists' convictions or theoretical apparatus

Taxonomy of interpretation biases

- *Confirmation bias*—evaluating evidence that supports one's preconceptions differently from evidence that challenges these convictions.

- *Rescue bias*—discounting data by finding selective faults in the experiment

- *Auxiliary hypothesis bias*—introducing ad hoc modifications to imply that an unanticipated finding would have been otherwise had the experimental conditions been different.
- *Orientation bias*—the possibility that the hypothesis itself introduces prejudices and errors and becomes a determinate of experimental outcomes.

Mechanism bias—being less skeptical when underlying science furnishes credibility for the data.

"Time will tell" bias—the phenomenon that different scientists need different amounts of confirmatory evidence.

The above categories of potential biases all occur after data are collected.

Many factors may introduce bias into the interpretation of data. Financial conflict of interest is one of these factors that may or may not be hidden from the reader or consumer.

- Transparency of COIs responds to one of the core ethical issues in science and medicine. But unless transparency results in behavior change, it does not address the issues of bias and public trust. Consider the case of COIs in the judicial system. According to the American Bar Association's Code of Judicial Conduct, the appearance of a conflict of interest must be avoided. In his essay *Law's Blindfold*, David Lisbon asks: why prohibit mere appearances of a conflict of interest?

“The theory is that the appearance of impropriety is almost as bad as impropriety itself, because—as the old saw puts it—justice must not only be done, but be seen to be done. Unless judges avoid the appearance of impropriety, public confidence in the fair administration of justice will be undermined.”

- Consider the case of a judge who makes the following declaration to his/her courtroom prior to announcing the prison term a convicted felon will receive:

"I will be sentencing the defendant, who has now been tried by his peers, to be incarcerated in a for-profit prison in which I have an equity interest. The extra money I earn from this partnership between my court and a reputable penal institution helps to compensate my low salary and allows me to serve the public interest and render more thoughtful and objective decisions."

GRAS and COI: Points to Consider

Nancy J Rachman, PhD

Pew COI/GRAS Workshop

August 7, 2013

Disclosures

- Presenting my personal viewpoints on GRAS, having reviewed Pew's COI reference documents
- No financial COI
- Scientific perspective:
  - Training: biology, physiology, risk assessment
  - Experience
    - Primarily private sector work
    - Regulation and risk assessment/safety evaluation of chemicals (including food additives, bioactive food ingredients, contaminants, pesticides)
    - Have directed GRAS evaluations, coordinated expert panels

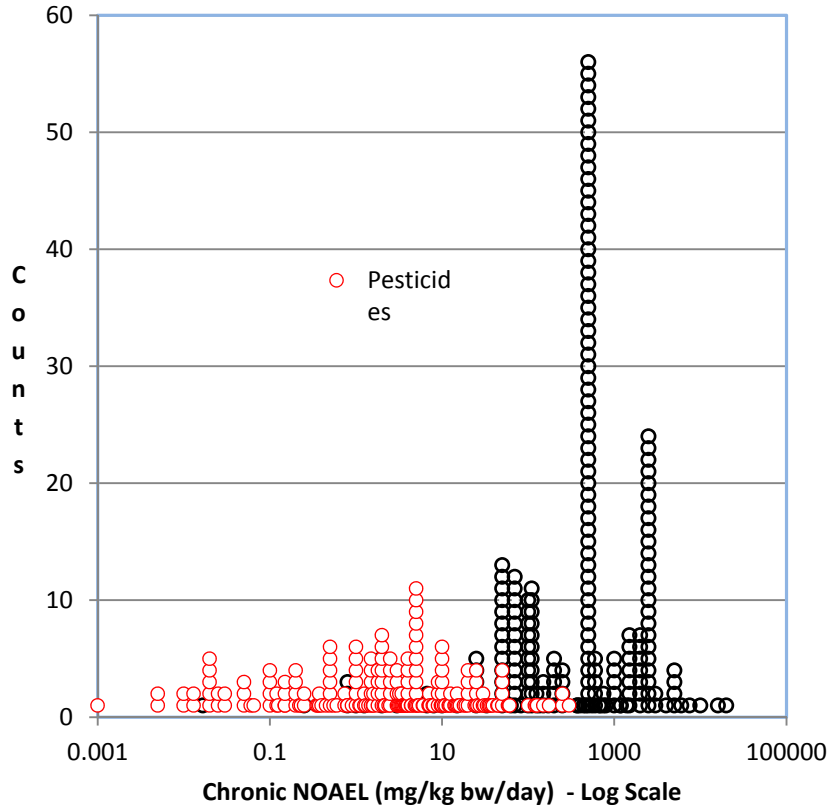
Factors Contributing to Confidence in Any Science-based Regulatory Decision

1. Managing potential for expert bias due to financial COI
2. Communication, transparency to minimize misunderstanding
   - COI concern appears to vary inversely with transparency
3. Ensuring integrity of the scientific basis for the decision

GRAS has some significant transparency challenges

Examples of Things We Have Not Made Transparent

1. Low relative hazard potential of many food substances vs other substances
   - For some classes ADI is not even established because highest possible doses produce no adverse effects



Examples of Things We Have Not Made Transparent, cont'd

2. The science behind a legally compliant (ie, properly done) GRAS determination

- A *regulatory compliance* activity that adheres to well-established rules and principles
  - FDA 1997 Proposed GRN rule should be finalized, and guidance, precedents consolidated
  - "Generally Recognized" means use of widely-accepted food safety evaluation/risk assessment approaches (eg, Redbook, JECFA)

GRAS and COI – General Thoughts

1. GRAS is a legally mandated activity of a regulated entity
   - Manufacturer has ultimate responsibility/accountability for both regulatory compliance and the safety of the substance-use
   - Any/every safety decision a company makes has a direct effect on its business

General Thoughts, cont'd

2. GRAS evaluations are not all alike

- Should prioritize different types of GRAS evaluations for COI attention
  - Sort/rank based on characteristics of substance (hazard) and proposed use (exposure)
- Specifically allow flexibility in approaches to dealing with experts, including COI

Allow Flexibility, cont'd

- Approach to any particular ingredient-use affirmation is a multifactorial decision involving both scientific and business considerations (e.g., whether to submit GRN)
- GRAS affirmations comprise a continuum of complexity; not all scenarios prompt the same COI concerns.

Continuum of Complexity

- FDA categorization of scope of GRAS situations:
  - Substance new to food
  - New use
  - Increased usage level
  - Significant manufacturing change
  - New safety evidence
- Within each is a continuum of complexity as to the safety question(s) to be addressed

Low/no Scientific Complexity

- "Routine": clear-cut safety question; approaches and calculations well established (eg, FDA, JECFA); internal regulatory compliance/safety expert responsible and accountable for compliance. Examples:
  - Change of supplier or manufacturing process for ingredient already in use;
  - Insignificant increase in the use level of an existing processing aid (no residues in final product);
  - Pharmacologically insignificant substitution (K+ for Na+ in a chemical salt).

Draft Guidance, Q 1: Does the expert have the necessary expertise

- Need flexibility as to experts, based on the nature of the safety question
- Need 2 kinds of expertise
  1. Subject matter expertise (depends on the safety question(s) raised)
  2. Food safety evaluation/risk assessment and GRAS process expertise
  3. Subject matter experts may serve as non-voting "advisers"

Question 3: Is the expert disqualified by serious COI?

- Is FDA 2008 guidance a good model to use?
  - FDA 2008 applies to ensuring the integrity of service of experts invited to participate in advisory committees subject to the Federal Advisory Committee Act (FACA) (5 U.S.C. App. 2).
  - GRAS is a compliance matter for a regulated entity
- One aspect that FACA advisory committee and GRAS panel do share: need confidence in the scientific integrity of the group's advice.

How best to promote this?

Questions 2 and 4: expert objectivity and independent judgment

These questions in the Draft connect to the science of the GRAS determination so deserve cautious analysis

- Subject matter specialization
- Scientific perspective the expert brings to bear on a safety question (aka “bias”)
- “Scientific consensus” in the context of GRAS

Objective should be both *scientific quality* and *scientific integrity* in the affirmation

GRAS and "scientific consensus"

- Does General Recognition require "consensus of the scientific community"???
  - A GRAS panel must be able to conclude that peers in the *specific scientific community of food safety evaluation* and related disciplines would generally agree with their conclusion that the substance is safe for the intended use, because of the manner in which their safety conclusion was reached
    - Includes approaches to selection, analysis, interpretation, weighting of evidence used

Getting the right expertise

- Affiliation- or service-based exclusion of experts seems like a substitution of other biases
  - GRAS example: expert whose research is funded by the sponsor company may have critical, specialized expertise (eg, behavior of the substance in the specific matrix of the specific product formulation)

Getting the right expertise, cont'd

- Other approaches are possible
  - FDA 2008, Step 9 – "Needs Analysis": A framework that makes a decision process more transparent/documentable/possibly disclosable
    - *Is the individual's participation necessary to afford the advisory committee essential [expertise]?*
  - GRAS panels do often have both voting and nonvoting experts (similar approach used by JECFA)

Ensuring the Scientific Integrity of GRAS Affirmations

- Food for thought: IOM 2009, Chapter 7, COI in the development of clinical practice guidelines: "systematic reviews" of clinical trial data to support health intervention recommendations (aka "evidence-based medicine")
  - *(p 203:) "The adoption of explicit, systematic methods for reviewing evidence and developing and documenting practice guidelines is…an important strategy for bias, whether the source may be intellectual and professional preconceptions, financial interests, or something else…*
  - *(p 207:) Arguably the most important steps are the conduct of a systematic review of the evidence and the linking of the recommendations to the evidence in an explicit fashion."*

Ensuring the Scientific Integrity of GRAS Affirmations

- A compliant GRAS determination is a systematic , evidence-based evaluation
- A compliant GRAS determination has an explicit approach and decision rules for selecting, evaluating and weighing evidence
  - These are not readily available in one place and not transparent, especially to nonspecialists

Hogan Lovells

The GRAS Process from a Food Industry Lawyer's Perspective

Martin J. Hahn
Hogan Lovells US LLP

Date: August 7, 2013

Food and Agriculture Group

Disclosure

- I am volunteering my time for the preparation and attendance at today's meeting
- My firm and I represent numerous food companies, trade associations, and other entities affiliated with the food industry

Common Agreement

- Foods and food ingredients introduced into commerce must be safe
- Foods and food ingredients must comply with relevant premarket authorization requirements
- The industry and regulators benefit through increased transparency
- The GRAS notification program at FDA has facilitated these objectives

What is GRAS?

- GRAS is a legally established concept
  - Food additives require FDA review
  - GRAS ingredients do not
- Are GRAS panels required to support a GRAS determination?
  - Absolutely not
  - If data support GRAS status on basis of common use in foods or scientific procedures, the ingredient is GRAS as a matter of law

GRAS Provides Needed Flexibility

- The food additive definition is so broad that it encompasses essentially every component added to food, including staples such as flour, vegetable oils, fruits, vegetables, spices, salt, pepper, vinegar, baking powder, baking soda, yeasts, and many other ingredients commonly found in pantries
- 20 years ago, quinoa had limited or no market penetration in the U.S.
  - Should companies have been forced to convene a GRAS panel before marketing it?
  - How about a hydrolyzed quinoa protein?

Robust Safety Standard for Food Additives and GRAS

- Regulatory definition of “safe” or “safety” at 21 CFR 170.3(i):

  “there is a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use. It is impossible in the present state of scientific knowledge to establish with complete certainty the absolute harmlessness of the use of any substance. Safety may be determined by scientific procedures or by general recognition of safety.”

Publication: Creates and Added Burden for GRAS Ingredients

- Same safety standard applies to food additives and GRAS ingredients on the basis of scientific procedures (21 CFR 170.30(b))
- The primary studies for GRAS ingredients, however, must be published
- In the absence of publication, the FDA position is clear: the ingredient cannot be GRAS

Enforcement Powers

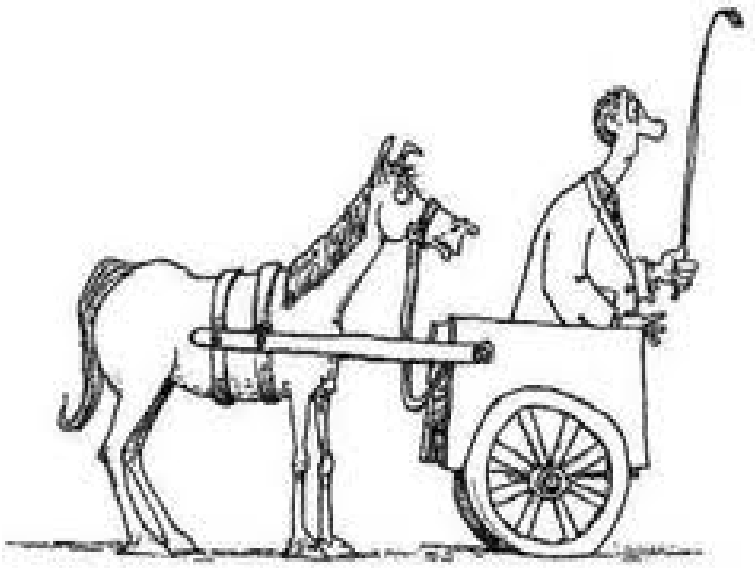
- FDA has the tools to monitor and confirm compliance
- The introduction into commerce of an unapproved food additive (i.e., an ingredient that is not GRAS) renders a food adulterated
- FDA has many tools in its enforcement tool box

Conflict of Interest?

- GRAS is a well-understood concept
- Through the Red Book and Guidance, FDA has provided clear criteria on the data needed to support GRAS status on basis of scientific procedures and common use in foods
- Want people making GRAS assessments who are familiar with the criteria established by FDA
  - Company employees
  - Consultants
  - Academia
  - Legal professionals
- FDA does not simply “rubber stamp” notifications—the agency takes a serious look at them and the underlying data

Conflict of Interest

- The issue is not “who” is making the decision but whether the decision will withstand FDA and judicial scrutiny
- To the extent there is a concern with the GRAS process, the concern seems more grounded in the manner in which self-assessments are made rather than who is making them



Disclosure over Disqualification

- To the extent FDA feels some type of guidance is necessary on “conflicts of interest,” the agency should opt for disclosures over disqualification
- Query: Does FDA have the legal authority to issue conflict of interest guidance on GRAS panels, particularly when there is no requirement for companies to convene GRAS panels?

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Morgan Lewis

Why is GRAS Different?

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August 7, 2013
Pew Charitable Trusts

Disclosure

- My firm and I represent food companies and trade associations
- I am a professional member of IFT and have served on IFT Divisions and Committees

Generally Recognized as Safe

- Statutory basis - Sections 201(s) and 409 of the Federal Food, Drug, and Cosmetic Act
- The term “food additive” means any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food …
- … if such substance is not generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or, in the case of a substance used in food prior to January 1, 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended use

Safety

- 21 CFR 170.3(i)
- …reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use. It is impossible in the present state of scientific knowledge to establish with complete certainty the absolute harmlessness of the use of any substance. Safety may be determined by scientific procedures or by general recognition of safety…

Generally Recognized as Safe

- 21 CFR § 170.30

- (a) General recognition of safety may be based only on the views of experts qualified by scientific training and experience to evaluate the safety of substances directly or indirectly added to food. The basis of such views may be either (1) scientific procedures or (2) in the case of a substance used in food prior to January 1, 1958, through experience based on common use in food. General recognition of safety requires common knowledge about the substance throughout the scientific community knowledgeable about the safety of substances directly or indirectly added to food.

- (b) General recognition of safety based upon scientific procedures shall require the same quantity and quality of scientific evidence as is required to obtain approval of a food additive regulation for the ingredient. **General recognition of safety through scientific procedures shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data and information.**

- (c) and (f), general recognition of safety through experience based on common use in foods requires a substantial history of consumption for food use by a significant number of consumers.

Key Considerations

- GRAS is a very high standard of evidence
  - "ordinarily be based upon published studies which may be corroborated by unpublished studies and other data and information."
- Substances at issue are:
  - Low hazard potential
  - Exposure
- Not all GRAS substances are the same
  - Different groups of substances have different characteristics
  - Use – exposure, presence (or absence) in food
- GRAS Substances are NOT Pesticides
  - EPA regulatory framework not a benchmark
  - Different considerations in terms of substance, hazard and exposure

COI and GRAS

- As with GRAS substances - all conflicts are not the same
  - Substances with no upper ADI?
  - Manufacturing/processing changes?
  - *de minimis* exposure?
- Not all conflicts are problematic or result in bias
  - Long term interest of industry and scientists
  - Standard procedures to address potential conflicts
  - Transparency and disclosure
  - Legal obligations

COI and GRAS

- Flexibility is required in proportion to relative risk
- Rigid standards for Advisory Committees do not translate directly to GRAS assessment
- GRAS Notifications are public
- All data and references are available on fda.gov
- Experience does not equal bias
- Documentation of assessment – systematic review
- Disclosure – e.g. 21 CFR Part 54

GMA

Representing the Makers of the World's Favorite Food, Beverage and Consumer Products

Experts and Conflict of Interest

August 7, 2013

Safety is Important to Food Industry

- There is nothing more important to GMA members than consumer safety: Good companies have a long history of producing safe food
- Providing unsafe, poor quality products results in loss of customers, declining reputation, and possible legal and regulatory actions
- GRAS regulations provide an important framework for safety assessment of new food ingredients and new uses of current ingredients
- The industry is working collaboratively to improve it

Production of Safe Products=Business Success

- Successful businesses produce products that consumers trust:
  - Safe
  - High quality
  - Meet a need
  - Good value

Food Producers are Responsible for Safety

- By law, responsibility for food safety falls on producers, manufacturers and importers
  - Safe for intended use
  - Warn consumers about potential risks
  - Provide information to help consumers understand risks and manage them effectively
  - Monitor the safety of products
  - Take corrective action if a safety problem is found

Conflict of Interest

- A set of circumstances that creates a risk that professional judgment or actions regarding a primary interest will be unduly influenced by a secondary interest
  - *Primary interest* refers to the principal goals of a profession or activity
    - Protection of clients
    - Health of patients
    - Integrity of research
    - Duties of public office
    - **Ensuring product safety**
  - *Secondary interests*
    - Financial gain
    - Motives as the desire for professional advancement
    - Wish to do favors for others

In the Case of GRAS

- Primary interest: Determine whether proposed use of a substance in food is generally recognized as safe by experts qualified by scientific training and experience to evaluate safety of food and food ingredients
  - Scientific procedures
    - Technical evidence of safety + Common knowledge
  - Common use in foods prior to 1958
    - Substantial history of consumption by significant number of consumers; may include technical evidence of safety
- Secondary interest: That an expert or panel of experts may be influenced to determine that the proposed use of a substance is generally recognized as safe when, in fact, the use is unsafe
  - Financial gain
  - Desire for professional advancement
  - Recognition for personal achievement
  - Favors to friends

Food Manufacturers Do Not Want Safety Issues Associated With Their Products

- Injured consumers
- Lost consumer trust
- Lost business reputation
- Distraction and cost
- Decreased sales, profit and shareholder value
- Legal action
  - Lawsuits: compensation for injury and damages
  - Criminal prosecution
  - Imprisonment
- Business collapse

Consequences to Employees of Businesses That Fail to Correctly Assess Safety

- Lost employment
- Lost benefits
- Lost short and long-term financial rewards
- Living with the consequences of getting it wrong
- Business collapse

Consequences to Consultants Who Fail to Assess Safety Correctly

- Decreased trust and credibility
- Lost reputation
- Business stress and failure
- Potential legal action
  - Malpractice
  - Criminal prosecution and imprisonment

Secondary interests

Secondary Interest	Reality
• Professional Advancement and recognition for achievement	• Lost employment • Lost professional reputation
• Financial Gain	• Lost employment • Decreased shareholder value • Lost short and long-term financial rewards
• Doing favors for others	• Business failure • Living with the consequences of getting it wrong

Good Businesses Implement Processes to Prevent CoI in Safety Assessments

- Codify the importance of safety in documented statements of principles, values and purpose
  - Commitment from the top to do the right thing
  - Reinforce commitment throughout organization
- Implement management systems to ensure development of safe products
- Employ qualified staff
- Design safety into all products, manufacturing and distribution
- Monitor market place performance and correct issues
- Audit compliance with management systems (internal, external and regulatory)
- Provide mechanisms for expression of employee concern

Underperforming businesses present a challenge

- True for all sectors, not just food
- Issues:
  - Lack capability
    - Do not know the law a/o regulations
    - Do not have safety expertise
    - Not aware of consequences of poor practice
  - Unlawful and unscrupulous activity

Trade Association Activities to Build Capability

- Recognize there is opportunity for improvement in all business processes including GRAS determinations
- Industry initiatives
  - Raise the bar through establishment of new industry standards
    - Code of Practice
    - Transparency principles
  - Educate members on requirements and effective GRAS assessment procedures
    - Seminars
    - Publications
    - Symposia and workshops
  - Establishing academic Center For Ingredient Safety And Risk Assessment

Trade Association Activities to Build Capability

- Establishing mechanisms to facilitate effective safety assessments
  - Increase visibility to GRAS ingredient usage
  - Safety re-reviews of existing ingredients and uses
  - Safety reviews of new ingredients and new uses
- Collaborating with stakeholders
  - Food and Drug Administration
    - FSMA Implementation
    - GRAS Determinations
    - Individual ingredient issues
  - Trade associations
  - Non-government organizations
  - Academic centers of excellence

Enforce Current Laws and Regulations

- GRAS regulations
  - Set a high standard
    - FDA can access GRAS determinations under current regulations if concerns arise
  - Enforcement is important
    - Maintain standards of practice
    - Regulatory action as needed
- FSMA will have an impact
  - Broadens the reach to similar affected foods
  - Third party auditors must report safety issues to FDA
- Industry has a role here also

Safety is Important to Food Industry

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- GRAS regulations provide an important framework for safety assessment of new ingredients and new uses
- The industry will work collaboratively to improve it

Flavor and Extract Manufacturers Association

FEMA Expert Panel Conflict of Interest Protections and Procedures

Trade Association Approaches to Conflicts of Interest

John B. Hallagan

Workshop on Potential Conflicts of Interest
in GRAS Decisions
The Pew Charitable Trusts
7 August 2013
Washington, D.C.

The Flavor and Extract Manufacturers Association of the United States

FEMA

- Established in 1909
- Based in Washington, D.C.

Over 130 members

- Flavor manufacturers
- Flavor users
- Others interested in flavors

FEMA

Primary activities

- FEMA GRAS Program
- Safety assessment of flavors
- Government relations

FEMA GRAS Program

- Established in 1960 – first Expert Panel
- Longest running industry GRAS program
- Legal and scientific aspects described in detail in various publications

How does the FEMA GRAS Program Work?

Candidates for FEMA GRAS status - only substances used to create compounded flavors including:

- Individual chemically defined flavoring substances
- Natural flavoring complexes
- Flavor enhancers/modifiers
- Flavor adjuvants

Conditions of intended use

- Human food only

How does the FEMA GRAS Program Work?

The FEMA GRAS program is open to FEMA members.

Member seeking a GRAS determination submits an application plus fee to the FEMA staff

- Pre-submission review is available.

If application is complete it is provided to the Expert Panel, along with supporting information, for review at a meeting of the Panel.

How does the FEMA GRAS Program Work?

FEMA Expert Panel reviews application and supporting information and renders a decision:

- GRAS, not GRAS, more information required

If GRAS:

- Applicant is notified.
- Decision is posted on the FEMA website.
- GRAS determinations published in *Food Technology*.
- Decisions and supporting information provided to FDA.
- Supporting information published in various forums including peer-reviewed literature and JECFA.

How does the FEMA GRAS Program Work?

Much information available from FEMA and in the literature on how the FEMA GRAS program meets the statutory requirements for GRAS.

- General recognition
- Among experts
- That the substance is safe through scientific procedures
- Under the conditions of intended use

How does FEMA protect against potential conflicts of interest and bias?

1. The Expert Panel is self-appointed. Panel members are not appointed by FEMA.

2. FEMA Expert Panel members are not allowed to be member company employees or have consulting relationships with member companies on issues related to flavors.

3. FEMA Expert Panel members provide a declaration of consulting and business relationships prior to meetings for review and action by the Panel's Legal Advisor. Actions may include mandated recusal.

How does FEMA protect against potential conflicts of interest and bias?

4. Expert Panel members do not know the identity of applicants who have submitted the application under review.

5. Applicants are not allowed to contact Expert Panel members or to attend Expert Panel meetings during which their applications are being considered.

6. Expert Panel members receive an honorarium from FEMA, not the applicants, for meeting attendance whether they determine substances are GRAS or not.

How does FEMA protect against potential conflicts of interest and bias?

7. FEMA Expert Panel members do not prepare GRAS applications.

8. The Expert Panel conducts their reviews during in-person meetings.

9. The identity of Expert Panel members is known to the public through regular publications.

10. FEMA staff members can't have independent consulting relationships with member companies on anything to do with the FEMA GRAS program.

For more information

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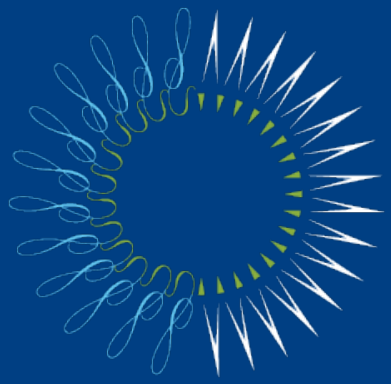

THE PEW CHARITABLE TRUSTS

Discussion Draft of Pew's "Guidance for Industry Selection of Experts Conducting GRAS Evaluations"

Tom Neltner

Project Director, Food Additives Project
The Pew Charitable Trusts

Overview

- Purpose
- But first . . .
- Four questions
- Exemptions
- Comparison to similar programs

Purpose of draft guidance

- Address shortcomings raised by Pew and U.S. Government Accountability Office (GAO)
- Provide FDA with specific language to implement recommendation from GAO in 2010 regarding Conflicts of Interest (COI).
  - GAO said FDA should develop a strategy to minimize the potential for conflicts of interest in companies' determinations.
- On 12/28/10, FDA requested comments on COI and other issues
  - 10 of 17 comments received addressed COI
  - All 10 supported FDA issuing guidance
  - 2 said FDA should only act if it felt guidance necessary
  - One suggested FDA consider clinical investigator standards at 21 CFR Part 54

But first . . .

- Unlike regulations, guidance documents are not binding
- Draft guidance would not apply to the following situations because they are not eligible for GRAS exemption:
  - Color additives, pesticides or animal drugs
  - Uses inconsistent with FDA's food additive regulations for specific additive use
  - Significantly different conditions of use from those allowed in FDA's GRAS affirmation regulations

Exemptions from proposed draft guidance

- When decision does not qualify for GRAS exemption
- When new use is within the same general food category and is performing the same physical or technical functional effect as an existing use (43 food categories at 21 CFR 170.3)
- If estimated daily intake is less than 1% of acceptable daily intake
- When change does not involve significant changes in the raw materials or increase in portion of particles less than 100 nanometers in size.

Key resources

- FDA's 2008 guidance on determining COI and eligibility for participation in its advisory committees
- Institute of Medicine's 2009 "Conflict of Interest in Medical Research, Education and Practice" Report
- Flavor and Extract Manufacturers Association's Expert Panel COI policy
- European Food Safety Authority's (EFSA) policy on independence and scientific decision-making processes regarding declarations of interests
- World Health Organization (WHO) policy on conflict of interest for expert committee on food additives

Four questions to industry should answer before selecting an expert:

- Does the expert have the necessary expertise?
- Do the experts have sufficient diversity of experience and knowledge to objectively represent the consensus of the scientific community?
- Is the expert disqualified because of serious financial conflicts of interest?
- Are there non-financial conflicts of interest that need to be considered?

Q1: Does the expert have the necessary expertise?

- Experts need to know FDA's guidance in their field
- Substance characterization needed for:
  - Substance not previously used in food
  - Significant manufacturing process changes
- Hazard assessment
  - Typically yes, especially when acceptable daily intake not generally recognized
- Exposure assessment
  - Typically yes, especially when estimated daily intake not generally recognized

Q2: Do the experts have sufficient diversity of experience and knowledge to objectively represent the consensus of the scientific community?

- Sufficient understanding of the broad scientific literature
- Aware of opinions or published articles, especially those with differing views.
- Not author of pivotal data. (The person could prepare dossier but not make decision.)

Q3: Is the expert disqualified because of serious financial conflicts of interest?

- Yes, if person would be disqualified because of a financial COI from serving on an FDA advisory committee
- Steps (see Appendix 2 for details):
  - Identify financial connections
  - Determine if decision would “direct and predictable effect” on those financial connections
  - Determine if there is a “disqualifying financial interest”
- Waiver option not available

Q4: Are there non-financial conflicts of interest that need to be considered?

- Knowledge of the identity of the firm (FEMA)
- Contact with firm during deliberations (FEMA)
- Expert testimony indicating bias to interests (WHO-JECFA)
- Other than a food safety organization:
  - Membership on managing body of a public or private entity with interest in decision (EFSA)
  - Membership on a scientific advisory body with a right to influence that body's decisions where body has interest in decision (EFSA)
- Providing advice even for free to trade associations with an interest in the decision (EFSA)

Next steps

- We plan to submit draft guidance on Monday, August 18
- If you send us your written comments by Wednesday, August 14, we will include them in our submission to FDA
- We will share with FDA copy of webinar and any written comments received

For more information on Pew's Food Additive Project

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