Four out of five doctors say that if they were stranded on a deserted island with no lawyers, they wouldn't need any aspirin.

American Medical Association

EPSTEIN BECKER GREEN

Good Reprint Practices

presented by

Bradley Merrill Thompson

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Topics

Part One **Background and context**

- **Conceptual**
- **Regulatory**
- **Constitutional**

Part Two **FDA's GRPs**

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Part Four **FDA's experience so far**

Part Five **What the future holds**

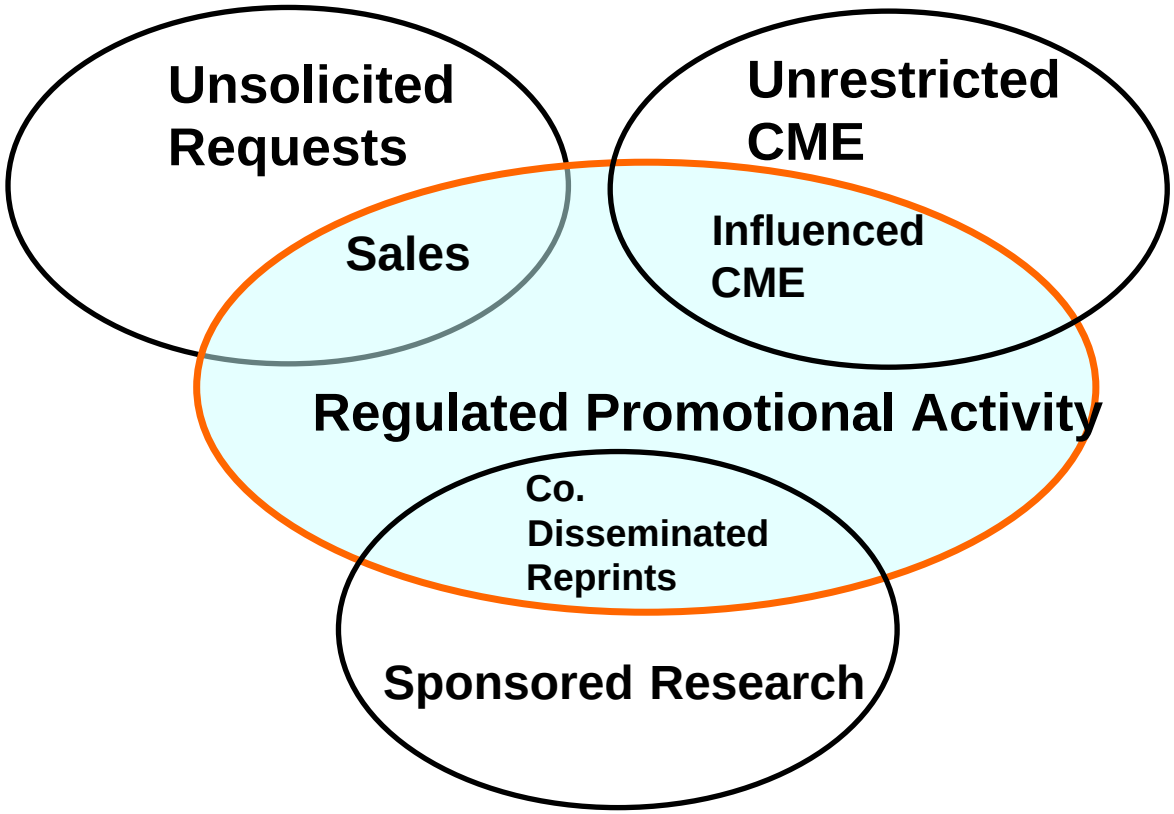
Conceptual Framework: Two Views

Q. How many fathers does it take to screw in a light bulb?

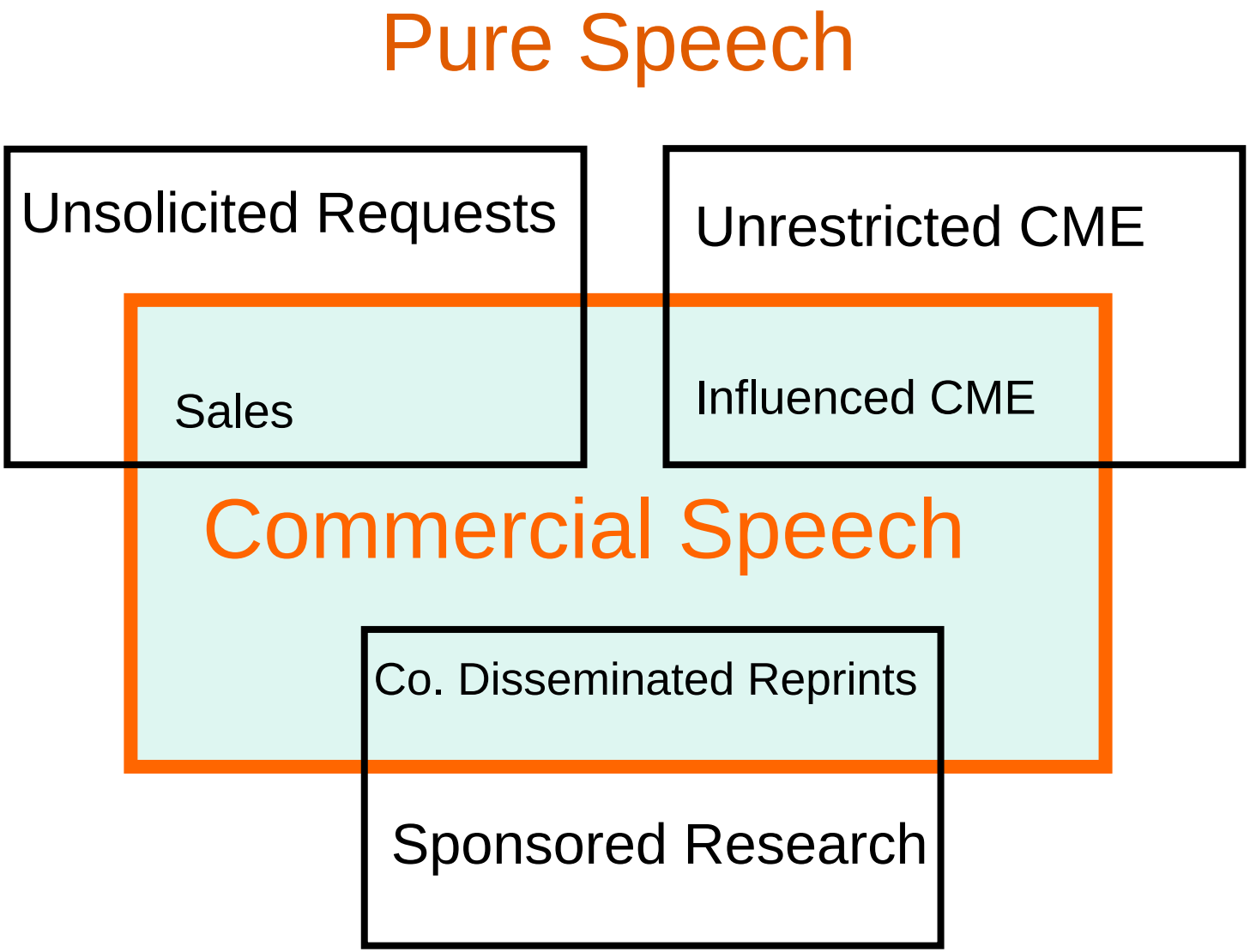
A. One. And he learned how by doing it every day at 4:00 AM before going to school, and paying his parents 5 cents for the privilege (a lot of money in those days.)

FDA View

Unregulated Scientific Exchange



First Amendment View



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Regulatory Framework

1. Basic Intended Use Framework
2. Evolution of the Legal Landscape

Basic Intended Use Framework

Under 21 CFR 801.4, the words “intended uses” … refer to the objective intent of the persons legally responsible for the labeling of devices. The intent is determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the article. This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives. It may be shown by the circumstances that the article is, with the knowledge of such persons or their representatives, offered and used for a purpose for which it is neither labeled nor advertised. …

Off-Label Use Rules: Basic Framework

- If an intended use is for other than the approved indication:
  - The lack of approval for the new indication makes the device "adulterated"
  - The lack of adequate labeling makes the device "misbranded"

The Ten Commandments contain 297 words.
The Bill of Rights 463 words.
The Gettysburg Address 266 words.
A recent federal directive to regulate the price of cabbage contains 26,911 words.

Evolution of the Legal Landscape

Where FDA was:

Strict regulation of off-label promotion

- FDA Guidances
  - Guidance on Dissemination of Reprints and Reference Texts (1996)
  - Guidance on Industry Supported Scientific and Educational Activities (1997)

Evolution of the Legal Landscape

Then FDAMA Section 401 (1997)

- Sets forth process for disseminating off-label information
- Requires disclosure statements & labeling
- Requires later filing for approval of any unapproved uses in the materials
- Sets forth audience restrictions
- Limited to dissemination of certain reference journals
- Now sunset

SEC Disclosure Requirements

- SEC's requirement that companies disclose material information to the investment community, including both positive and negative results of clinical trials, is often inconsistent with FDA's limitations on disclosure
  - Clash of pro-speech policy with FDA's speech restrictions
- SEC has brought enforcement actions against companies for failure to disclose important information about products in clinical trials

First Amendment

Q. What do you get when you cross the Godfather with a lawyer?

A. An offer you can't understand.

First Amendment

- FDA’s authority to regulate off-label promotion has been limited by the courts – any such regulation must be narrowly tailored to achieve FDA's purpose
- Cases:
  - Washington Legal Foundation v. Henney (2000)
  - Thompson v. Western States Medical Center (2002)

Washington Legal Foundation

- WLF brought action challenging 1996/1997 Guidances (and later, FDAMA) as unconstitutional under the First Amendment
- WLF won at trial
- On appeal, when FDA asserted they were not mandatory, but created only safe harbors, the court held the matter was not ripe for determination—a technicality

Washington Legal Foundation

- Trial court suggested restrictions of its own, which many manufacturers have adopted.
  - Articles from bona fide peer-reviewed journals or text books published by a bona fide independent publisher
  - Product must be cleared or approved for at least one indication
  - False and misleading materials still open to FDA enforcement
  - Must disclose off-label use
  - Must disclose any relationship between the company and product or authors

Western States

- Background: FDAMA exempted "compounded drugs" (mixed by pharmacist) if, among other things:
  - Drug is compounded by licensed pharmacist
  - Providers don't advertise or promote compounding of a particular drug, drug class or drug type
- Challenge:
  - Compounding provision challenged by group of pharmacies arguing provisions prohibiting advertising violated First Amendment

Western States

- U.S. Supreme Court held FDAMA compounding provision unconstitutional
- Lesson learned:
  - Government must use the least restrictive means possible to achieve its objectives
  - If government can achieve its purpose without restricting speech, or by restricting less speech, it must do so

Impact of the Litigation

- FDA cannot infringe on the right of medical device companies to promote their products if other, less restrictive measures can achieve FDA's objectives, such as:
  - Disclaimers and warning labels
  - Disclosures
  - Limitations on non-speech related activity
  - Narrowing of speech restrictions
- On May 16, 2002, FDA requested comments on its authority to regulate communications; More than 730 comments received
- Led to Good Reprint Practices

Evolution of the Legal Landscape

What the Law is NOW

- FDCA sections on misbranding are still in effect
- FDAMA 401 provisions on dissemination of off-label materials and regulations have sunset
- CME guidance is still in effect
- New guidance on journal reprints
- FDA cannot infringe on promotion of products if it has other options

Part Two: FDA's GRPs

Q. Why don't you ever see lawyers at the beach?

A. Cats keep covering them with sand.

FDA Guidance: Good Reprint Practices

- Published Jan. 2009
- An opportunity for medical device companies to hand out scientific reprints without causing the device to be misbranded, or otherwise constituting off label promotion
- Lots of strings attached
  - Publishing Organizations must be legit
  - Channels of Distribution must be legit.
  - Influence of the Manufacturer in the content of a reference publication must be avoided.

FDA Guidance: Good Reprint Practices

Content of Disseminated Information

- Must not pose a significant risk to the public health.
- Must address sound evidence.
- Must be truthful and not misleading.
  - For example, avoid information that is inconsistent with the weight of credible evidence
- Must be disseminated in its original state.

FDA Guidance: Good Reprint Practices

Manner of Dissemination

- The information must be accompanied by:
  - a copy of the approved product labeling;
  - a comprehensive bibliography; and
  - a publication representative of any articles reaching different conclusions.
- Dissemination must take place separate and apart from promotional activities.

FDA Guidance: Good Reprint Practices

Disclaimers and disclosures

- That the uses described in the article have not been approved or cleared by FDA
- The manufacturer's interest in the medical device
- Any author known to the manufacturer as having a financial interest in the manufacturer or the device
- All significant risks or safety concerns known to the manufacturer concerning the unapproved use that are not discussed in the article

Changes from proposed to final

1. Scope of “health care entity”
2. Scope of “adequate and well controlled investigations”
3. Scope of “false or misleading”
4. Use of representative publication
5. Nature of financial interest disclosure

IVD Specific Issues

- Applicability to
  - ASRs
    - Some at FDA say inapplicable
    - Brad asks why?
  - IUOs and RUOs
    - Some at FDA say inapplicable

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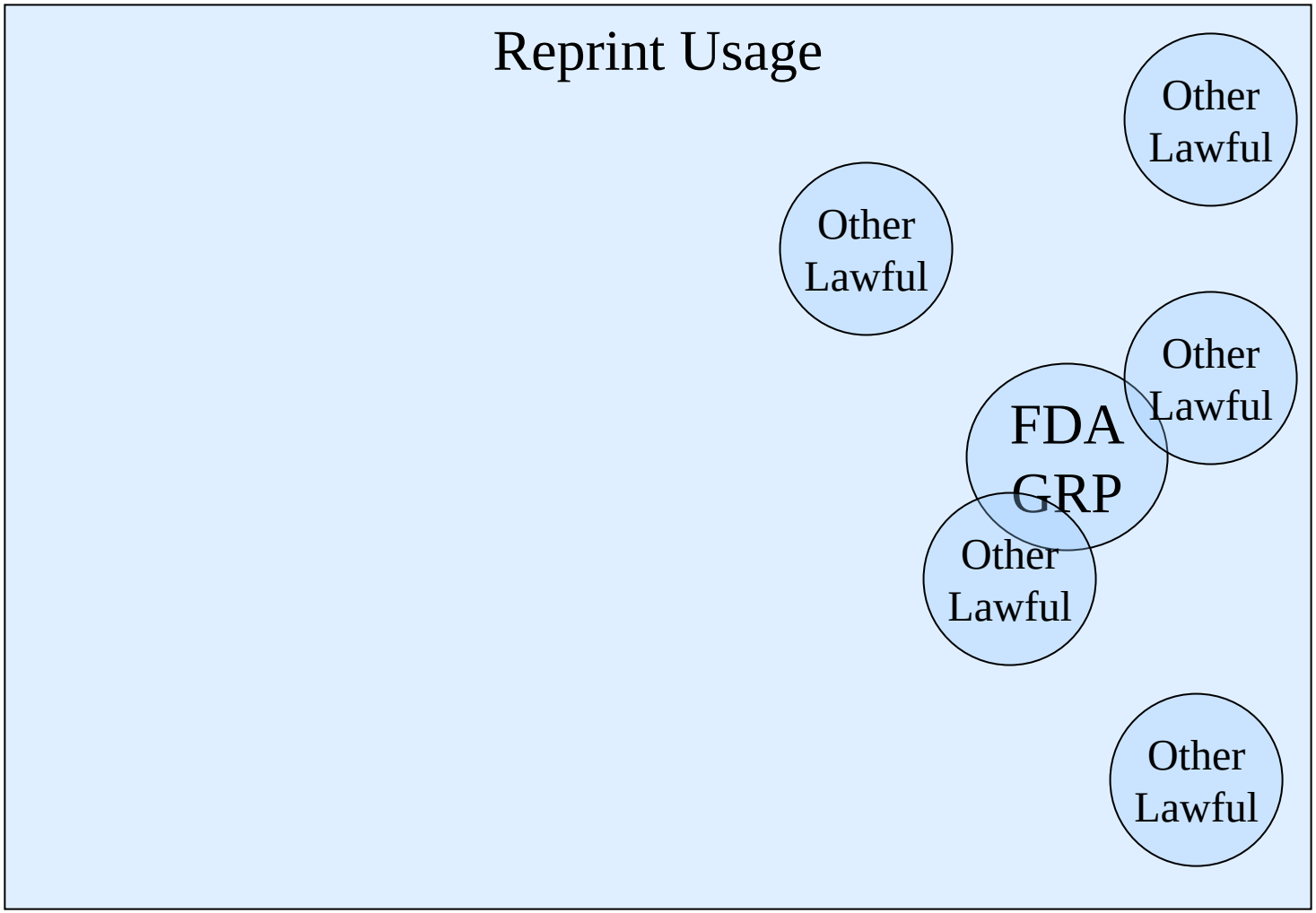
Part Three: Brad's GRPs

One way to make sure crime doesn't pay would be to let the government run it.

Ronald Reagan

More conduct is lawful than FDA indentifies



Brad's rule for indentifying other lawful dissemination

Taking all the relevant factors into account, is dissemination of the off label reprint in the best interest of the public health?

This is different than asking if such dissemination will help the company. On label reprints can play that role.

Factors to Consider for Reprints

1. Regulatory Status-- 510(k) or PMA or investigational
2. Type of Off Label Content
   a. Any new indications for use, or intended use?
   b. Any difference in directions for use?
   c. Any difference in performance claims made?
3. Public Health Value
4. Ability to Avoid Off Label Content
5. Regulatory History
6. Health Risk
7. Evidence Quality
8. Author Ties
9. Peer Review Process Robustness
10. Fair Balance
11. Disclosures and Disclaimers

Unsolicited Requests for Reprints

- When may off-label information be provided?
  - In response to an unsolicited request of a health care provider
- Best Practices:
  - Make sure unsolicited
  - Keep the discussion objective, non-promotional in nature, and fairly balanced
  - Confine responses to the specific question asked, narrowing broad questions before responding
  - Clearly disclose that the device has not been cleared or approved for the discussed use
  - Document all responses to unsolicited requests

Medical Affairs

- Long recognized by FDA as a position that has additional freedom to engage in *bona fide* medical and scientific exchange
- Should not report to marketing or sales—must remain independent
- Must maintain its credibility
- Must have medical/scientific credentials,
  - Education
  - Experience

Level Of Restriction For Peer-Reviewed

- Don’t use
- Medical fulfillment of unsolicited request
- Sales fulfillment of unsolicited request
- Sales dissemination with restrictions
- Sales dissemination without restriction
- Remember all options require training to do well

Process becomes paramount

- Do the company's SOPs applicable to the review and approval of reprints and accompanying materials address and create an infrastructure to support key issues such as:
  - Whether a journal article was published by an appropriate organization, comprised of experts in a relevant field, after undergoing an established peer-reviewed process;
  - Whether such an organization's editorial board maintains adequate policies and procedures for disclosing potential conflicts of interest of authors, contributors or editors;
- Does the manufacturer's review committee have expertise to properly evaluate the scientific integrity of clinical investigations described in a reprint according to the criteria specified in FDA's Reprint Guidance, including:
  - Whether a trial referenced in the reprint is adequately designed and conducted and well controlled;
  - Whether trial outcomes are consistent with those of a majority of similar recognized studies;
  - Whether trial findings have been widely supported or contradicted by experts in a relevant field; and
  - Whether a trial yields information that could pose a significant risk to public health?

More process

- Are SOPs applicable to distribution of reprints by sales representatives designed to address issues such as:
  - The appropriate form of a reprint;
  - The materials and information that must accompany a reprint (e.g., disclosures, labeling, bibliography, representative contradictory articles, etc.);
  - Requirements for distributing reprints separately from promotional materials, and prohibitions on discussing reprint content;
  - Appropriate recipients and venues for reprint distribution; and
  - Limitations on the frequency of distribution and categories of recipients?
- Does the manufacturer's audit agenda ensure the following:
  - Regular audits of all SOPs relevant to reprint practices to ensure continued compliance with FDA guidance;
  - Regular and periodic review of all reprints and accompanying materials being distributed to ensure that all distributed information is current and accurate?
- Does the manufacturer maintain records of all reprints and accompanying materials distributed, as well as distribution dates and the names and addresses of recipients?

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Part Four - FDA's Experience

The voters have spoken—the bastards.

Richard M. Nixon

FDA’s experience so far

- Little in devices,
  - and IVDs in particular

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Part Five: The Future

In Massachusetts it is illegal to keep a mule on the second floor of a building not in a city unless there are two exits.

Where we are today

- Basic principle: Truthful speech should be allowed
- Many argue that “truthful” should be judged in the eye of the audience
  - Doctors are sophisticated; they can be told the truth
  - Patients should be protected
- Begs the question, what level of substantiation is required to establish the truthfulness of a statement?
- But is handing a doctor a peer-reviewed article untruthful? Does it matter who hands it?
- FDA needs to protect the integrity of its clearance/approval process

Likelihood FDA will decide to modify

- New personnel in the Obama Administration make change more likely
- But I have heard no specific plans

The Future: Allergan vs. US

- Filed in DC in October, 2009
- Broadly opposes FDA regulation of off label information
- Challenges FDA's
  - Intended use regulation
  - Definition of labeling
  - Interpretation of false or misleading
  - Advertising restrictions
- Who knows what will happen

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Comments or Questions?

Arguing with a lawyer is like
mud wrestling with a pig: after a while
you realize that the pig actually enjoys it.