Managing Off-Label Promotion Risks

L. Stephan Vincze, J.D., LL.M., V.P., Ethics & Compliance Officer
Una Ortell, Director, Regulatory Affairs, Advertising & Promotion

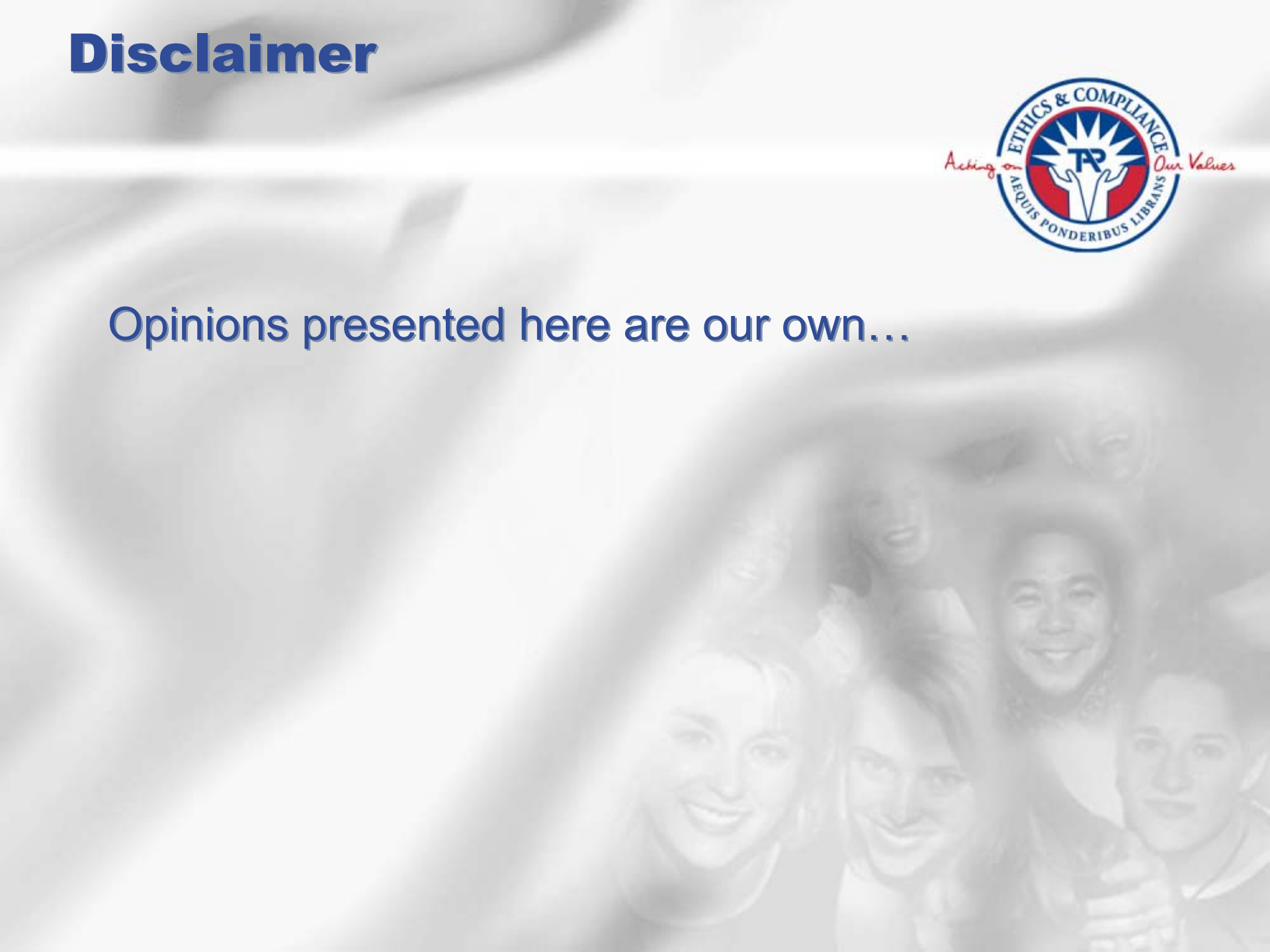
TAP Pharmaceutical Products Inc.

Overview

- Creating an Effective Compliance Framework -- TAP's Experience & Approach
- Risks of Off-Label Promotion
- Definition of Promotion
- On-Label vs. Off-Label
- How to Manage Off-Label Promotion Risks
- Scientific Exchange
- FDMA and the First Amendment
- CME
- Recommendations and Final Thoughts

Disclaimer

Opinions presented here are our own…



Food For Thought

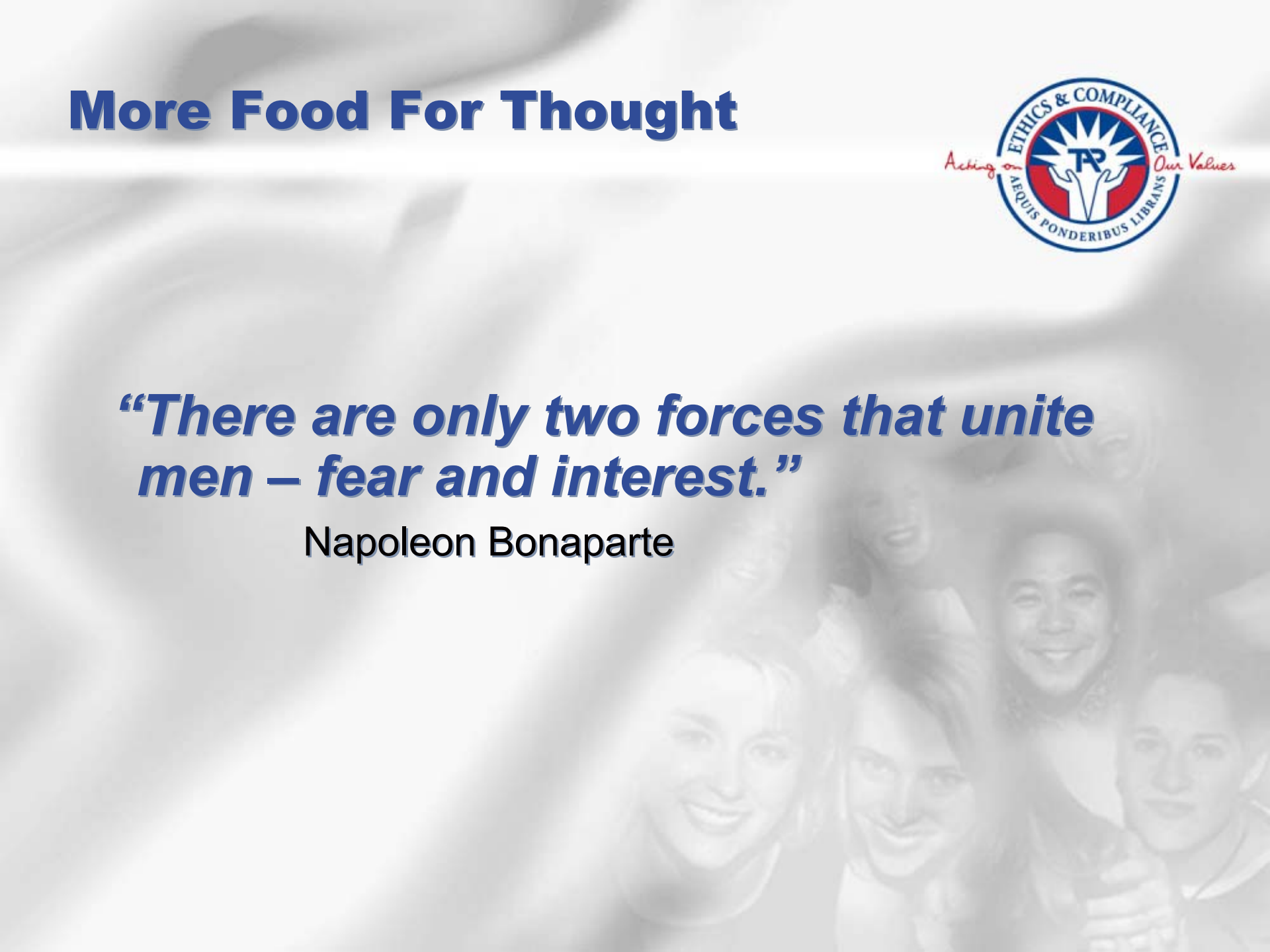
"*Wisdom comes only through suffering.*"

Aeschylus, Agamemnon, 458 B.C.

More Food For Thought

"There are only two forces that unite men – fear and interest."

Napoleon Bonaparte



Code of Medical Ethics -- History

- Oath of Hippocrates – 5th Century B.C.
  - Christianized in 10th or 11th Century A.D.
- Code of Medical Ethics, by Dr. Thomas Percival, 1803, England
- AMA Code of Medical Ethics, 1847, 1st Meeting in Philadelphia
  - Major Revisions: 1903, 1912, 1947, 1994

[From Code of Medical Ethics, 2004-2005 Edition, American Medical Association (AMA), page x.]

AMA Principles of Medical Ethics

Preamble

The medical profession has long subscribed to a body of ethical statements developed **primarily for the benefit of the patient**. As a member of this profession, a physician must recognize responsibility to patients first and foremost, as well as to society, to other health professionals, and to self.

[From Code of Medical Ethics, 2004-2005 Edition, American Medical Association (AMA), page xiv.]

The Relation of Law and Ethics

Section 1.02

…Ethical values and legal principles are usually closely related, but **ethical obligations typically exceed legal duties**. In some cases, the law mandates unethical conduct. In general, when physicians believe the law is unjust, they should work to change the law. In exceptional circumstances of unjust laws, the ethical responsibilities should supercede legal obligations…

[From Code of Medical Ethics, 2004-2005 Edition, American Medical Association (AMA), page 1.]

What Is an Ethics & Compliance Program?

The Process of

Ethics & Compliance

An ethics & compliance program is a centralized ***process*** to detect, correct and prevent illegal or improper conduct* **AND** to promote honest, ethical behavior in the day-to-day operations of an organization.

* U.S. Sentencing Commission

Creating an Effective Compliance Framework

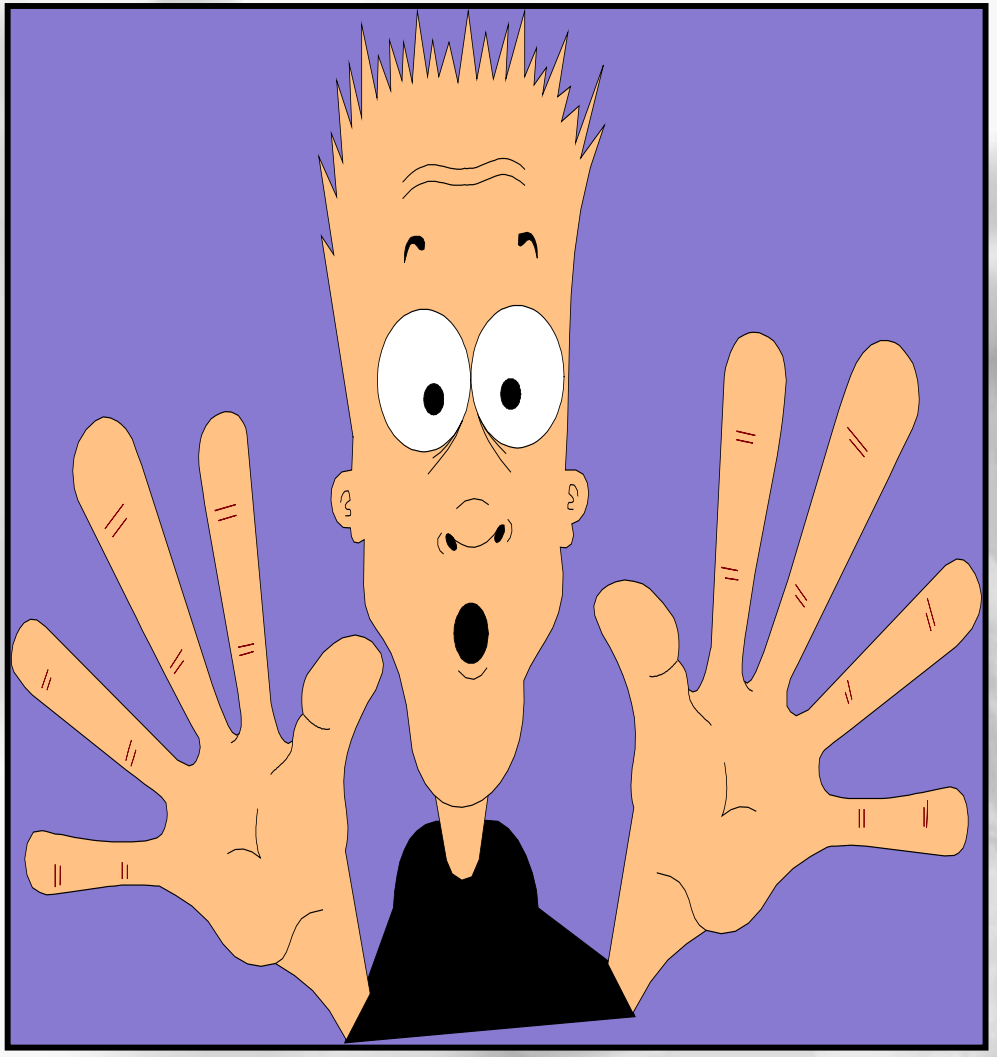
- Capture Minds and Hearts
- Structure that Emphasizes Partnership, Service and Value
- Striking the Balance Between Compliance Requirements and Business Objectives

Ethics & Compliance Team Mission Statement

The Mission of TAP's Ethics & Compliance Team is **to foster a culture of leadership and integrity that strikes the right balance** between meeting business objectives and compliance requirements through continued:

- **Adherence to high ethical standards**
- **Partnership**, customer service and continuous process improvement to:
  - Prevent, detect and correct inappropriate conduct
  - Enhance operational performance and compliance effectiveness
  - Provide timely business solutions with measurable results
  - Create an environment of open communications and fun
- **Recognized national leadership**

Reduce the **Fear Factor**



Guiding Principles For Effective Collaborations

- Focus on the patient, and quality science, medicine and education
- Establish clear goals and object
- Define deliverables
- Ensure transparency
- Open, clear communication
- Submit everything to the New York Times Test

Risks of Off-Label Promotion

- OIG
- FDA
- States
- Consumers

OIG Compliance Guidance
Risk Areas

1. Integrity of Data for State and Federal Payments
2. Kickbacks and Other Illegal Remunerations
   - Relationships with purchasers and their agents
     - Discounts and other remuneration to purchasers
     - Formulary and formulary support activities
     - Average Wholesale Price ("AWP")
   - Relationships with physicians and other persons and entities in a position to make or influence referrals
   - Relationships with Sales Agents
3. Drug Samples Laws & Regulations (PDMA)

DDMAC Enforcement Actions

- Untitled Letters formerly known as Notice of Violation Letters (NOV)
- Warning Letters
- Injunction/Consent Decree
- Seizure
- Criminal Action

DDMAC Recent Activity

- 1Q 2005 – 7 letters (3 warning)
- 2Q 2005 – 9 letters (5 warning)
- July 2005 – 5 letters (3 warning)

Protropin (somatrem for injection)

- Genentech – Settlement $50 million – admitted marketing drug for unapproved or off-label uses.
  - Investigation began in 1991 and concluded in 1999
- The unprecedented prosecution and fine, said FDA Commissioner Jan Henney, M.D., after the settlement was announced "sends a clear and strong signal that FDA takes very seriously promotions using illegal means."

Neurontin (gabapentin)

- Settlement $430 million for promotion of unapproved uses

What is Promotion?

- Activities/Materials intended to promote the sale of a drug product

On-Label vs. Off-Label

- On-Label: claims that are supported by substantial evidence or substantial clinical experience which are consistent with the product labeling
- Off-Label: claims that are not consistent with the product labeling
- Substantial evidence traditionally regarded as two adequate and well-controlled studies.

Unapproved Use

- Promotional activities are misleading if they suggest that a drug is useful in a broader range of patients or conditions than has been demonstrated by substantial evidence or substantial clinical experience.
  - Unapproved indication
  - Unapproved subset or subpopulation
  - Unapproved dose/frequency/route of administration etc

Best Way to "Manage" Off-Label Promotion Risk?

How to Prevent Off-Label Promotion?

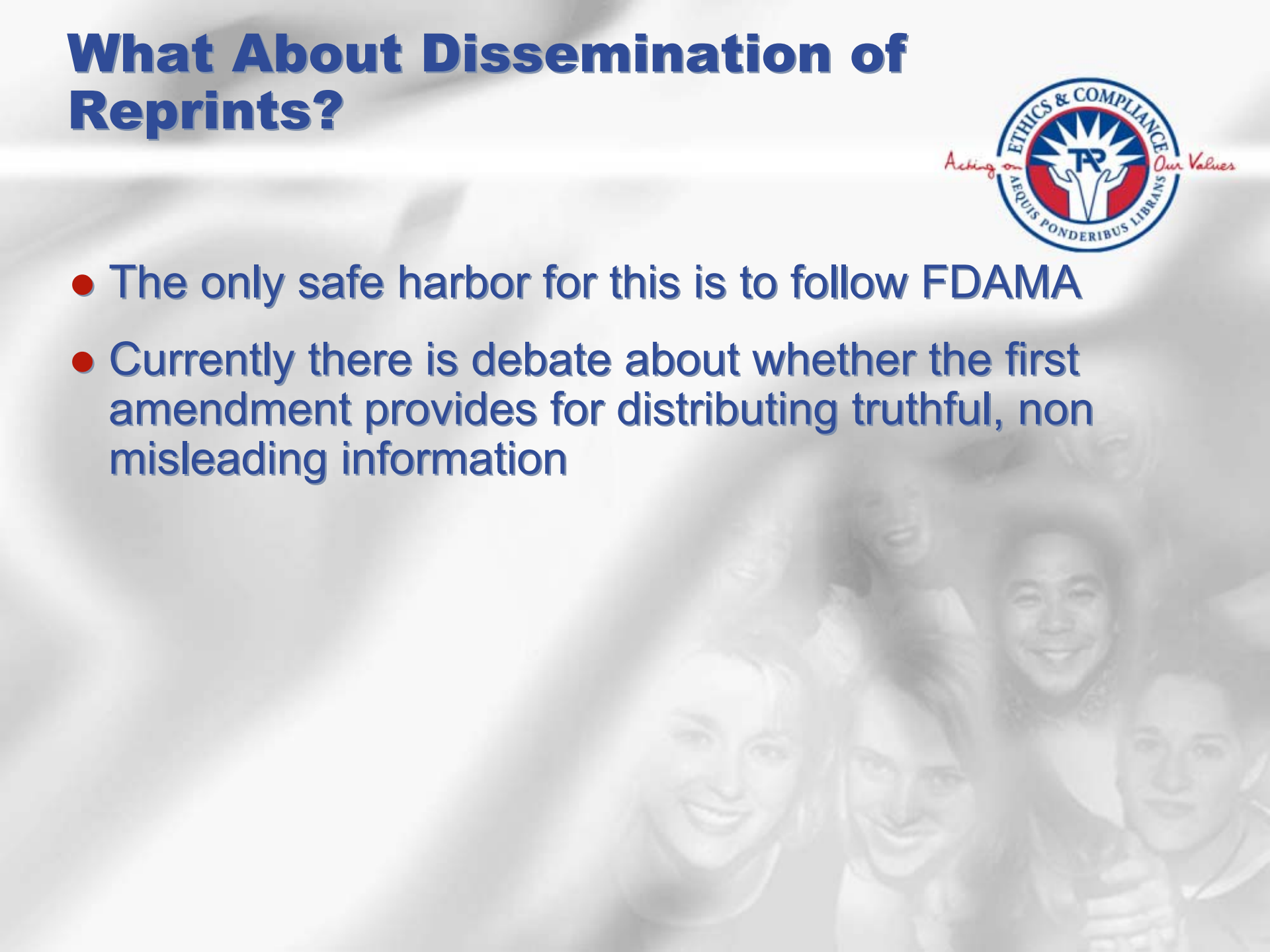
- Effective Compliance Framework
- Corporate policies regarding Legal/Medical/Regulatory review of promotional material
- Rigorous training of reviewers
- Rigorous training of sales representatives
- Appropriate disciplinary measures

What About Scientific Exchange?

- Scientific exchange is not promotion nor is it a clever way to conduct off-label promotion
- Allows for full exchange of scientific information including dissemination of scientific findings in scientific or lay media
- Does not allow for promotional claims of safety or effectiveness for a use which is under investigation
- Does not allow for commercialization of a drug prior to approval

What About Dissemination of Reprints?

- The only safe harbor for this is to follow FDAMA
- Currently there is debate about whether the first amendment provides for distributing truthful, non misleading information



1997 FDAMA

- The FDA Modernization Act of 1997 pertinent sections
- Modified the definition of “substantial evidence” in certain circumstances
- One adequate and well-controlled study may constitute substantial evidence as the basis for product approval
- Allowed for the limited dissemination of off-label reprints and reference texts

Dissemination of Information on Unapproved/New Uses

Allows a manufacturer to disseminate written information concerning the safety, effectiveness, or benefit of a use not described in the approved labeling for an approved drug or device.

Approved drug or device for Marketing by FDA

In the form of an unabridged peer reviewed reprint or reference publication

Limitation on Recipients

Allows for the restricted dissemination of off-label information to:

Healthcare practitioner, pharmacy benefit manager, health insurance issuer, group health plan, or Federal or State Government agency

Reference Publication

- Has not been written, edited, excerpted, or published specifically for, or at the request of, a manufacturer
- Has not been edited or significantly influenced by such a manufacturer
- Is not solely distributed through such a manufacturer, but is generally available in bookstores or other distribution channels where medical textbooks are sold
- Does not focus on any particular drug that are under investigation by a manufacturer
- Does not present materials that are false or misleading.

Acceptable Reprint

- Publication in a scientific or medical journal which utilizes an independent expert editorial board
- Journal articles are peer-reviewed
- Journal is generally recognized to be of national scope and reputation
- Journal is indexed in the Index Medicus of the National Library of Medicine of the National Institutes of Health
- That is not in the form of a special supplement that has been funded in whole or in part by one or more manufacturers

Information to be Disseminated

- Drug must be FDA approved
- Unabridged reprint or reference publication
- Does not pose a significant risk to public health
- Not false or misleading
- Not derived from a clinical study conducted by another company without permission from that company
- Must be scientifically sound i.e. **not** an abstract, letter to the editor, Phase I study (healthy subjects), observations in less than 4 people, or abridged article

Mandatory Statements and Information

- Disclosure regarding unapproved use
- Official labeling for product
- Bibliography of related articles
- Other financial disclosures

Manufacturer's Submissions, Requests and Applications

- 60 Days prior to dissemination
  - Company must submit identical copy of what will be disseminated to FDA
  - Other clinical trial information
  - Method for selecting article
  - All pertinent sNDA information – submit within 6 months if studies are done or 3 years if not

Recordkeeping and Reports

- Maintain records sufficient to allow for corrective action if requires
- Maintain an identical copy of the information disseminated under this part
- On a semiannual basis, submit to FDA a list of title of relative articles disseminated, category of recipients, additional ongoing research, periodic progress report on ongoing studies for the sNDA
- Records must be maintained for at least 3 years after cessation of dissemination

What about CME?

- Follow the guidance document (12 steps)
- Make sure it is independent
- Use reputable company
- Have credible separation from Sales/Marketing
- Ensure that the intent is not to promote off-label
- Focus on quality science, medicine and education -- *for the purpose of education NOT promotion*!

What About Disease State Information?

- Good to do, if it is done correctly
- Should not have the same look and feel as promotional materials for drug
- Should be truthful, accurate and not misleading
- Great for both consumers and HCP
- Again, not a sneaky way to promote your product.
- Follow the guidance from DDMAC

Recommendations

- Establish an effective Compliance Framework
- Weave compliance into the fabric of your organization
- Focus on the patient and quality science, medicine and education
- Sponsor quality, credible CME programs
- Understand that the best way to manage off-label promotion risk is not to do it!
- Do not do it openly or covertly
- Make sure that everyone in the company understands this and operates accordingly.
- If it doesn't feel right, it probably isn't

CREDIBILITY
Is The Key To Effectiveness!

Final Thoughts

Good ethics & compliance

is good business!

Questions/Answers

Contact Information

Steve Vincze

Vice President,

Ethics & Compliance Officer

TAP Pharmaceutical Products Inc.

675 North Field Drive

Lake Forest, IL 60045

Tel. (847) 582-6301

Fax. (847) 582-5006

e-mail: steve.vincze@tap.com

Thank You!


ETHICS & COMPLIANCE
AEQUIS PONDERIBUS LIBRANS
TAP
Acting on Our Values