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FDA PROMOTIONAL RULES

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- A drug manufacturer may not promote a drug for a use that FDA has not approved
- Dissemination of information about an unapproved use does not always run afoul of FDA's rules
  - -- Responses to unsolicited physician questions
  - -- Medical education and "scientific exchange"
  - -- Peer reviewed, independent journal articles
- But disseminating company-produced off-label claims to physicians or advertising off-label uses to consumers will be viewed by FDA as violative
- Dissemination of information about an unapproved use by or on behalf of a manufacturer can have consequences beyond FDA regulatory action

The Basic FDA Rules for Rx Drug Promotion

- FDA approved labeling (the PI) is the regulatory point of reference
- Promotional materials must be consistent with the FDA-approved labeling
- Claims may not be false or misleading or lacking in fair balance

How FDA Assesses Promotional Materials

- Submission at time of first use (2253 Form)
- Submission of launch materials (optional)
- FDA oversight and monitoring
  - -- labeling
  - -- mailers (Dr. Healthcare provider letters)
  - -- brochures
  - -- reprints
  - -- exhibits
  - -- websites
  - -- sales aids
  - -- press materials
  - -- SEC submissions (mandatory disclosure of material information?)
  - -- advertising (journals, magazines, TV ads)
  - -- non-print evidence of intended use

What is FDA Looking For?

- Unsubstantiated comparative or superiority claims
- Claims that are misleading by omission
  - -- Failure to reveal important risk or safety information
  - -- Minimizing warning information
  - -- Failure to reveal limitations on use
- Implied claims of broader indications, broader conditions of use, larger patient population
- Drug-of-choice claims
- Misleading DTC ads
- Company compensation schedules and marketing plans

Where Does the First Amendment Come In?

- Drug promotional material is commercial speech
- Regulation of commercial speech based on four questions
  - -- Does the speech concern a lawful activity and is the speech false or inherently misleading?
  - -- Is the government's interest in regulating (restricting or limiting) the speech substantial?
  - -- Does the regulation of the speech directly advance the government's interest?
  - -- Is the regulation more extensive than necessary to serve that interest? ("If the government can achieve its interests in a manner that does not restrict speech, or that restricts less speech, the government must do so." *Thompson v. Western States*)

FDA's First Amendment Interests

- FDA has a substantial interest in preserving the integrity of the drug review process by requiring manufacturers to demonstrate the safety and effectiveness of claims in order to get them approved (on-label)
- Restricting off-label use directly advances FDA's interest in promoting on-label use of drugs
- Are FDA restrictions more extensive than necessary?

  -- It depends

Where the First Amendment Balance Stands

- As a result of court decisions, it appears that companies can disseminate copies of peer-reviewed journal articles to doctors, or disseminate portions of bona fide, independently published textbooks to doctors
  - -- If the company also disseminates the PI, discloses that the use discussed in article/text is not approved, and discloses the manufacturer's support for the work that is reported in the article/text
- Companies can sponsor CME where off-label uses will be discussed

Where the First Amendment Balance Stands [cont'd]

- Doctors can lawfully prescribe a drug for an off-label use
- A claim may be inherently misleading when addressed to non-physicians
- Truthful, non-misleading information is not fully protected
  - -- *U.S. v. Caputo*, D.N.J. 2003 -- off-label prosecution permitting defendants to engage in all forms of truthful
  - -- Non-misleading off-label promotion would frustrate FDA's ability to evaluate the effectiveness of off-label uses
  - -- Manufacturers would seek FDA approval of only those uses which could be approved easily and inexpensively
  - -- Court is "unable to identify a less burdensome alternative that would advance the government's substantial interest. Thus, the FDA prohibitions are not more extensive than necessary."

- FDA notice of March 2000 regarding off-label use
- FDA enforcement on case-by-case basis (DDMAC)
- October 2003 Compliance Policy Guide (Marketed Unapproved Drugs)
- Regulatory focus on misleading statements

New Challenges of Off-Label Promotion

- Causing the submission of a false claim under the False Claims Act (*Franklin v. Parke-Davis)*
  - -- Submission for payment of off-label prescription (a not-covered outpatient drug) is a material misrepresentation to obtain a government benefit
  - -- Off-label prescription submitted for reimbursement by Medicaid can be a false claim under the FCA
  - -- Where the manufacturer's knowing conduct "causes" the submission
  - -- "Causing" may be based on reasonably foreseeable submissions
  - -- Truthful off-label promotion and improper financial incentives (such as kickbacks) are enough

False Claims Act Exposure

- Violations of FCA -- $5,000-$11,000 per false claim
- Violations of FDCA
- Related risks
  - -- Exclusion from healthcare reimbursement programs
  - -- Corporate Integrity Agreements
  - -- State unfair trade practice laws
- “Implied Certification”
- Neurontin settlement

New Players -- Who Sets Federal Healthcare Policy?

- Whistleblowers (*Franklin)*
  - -- Qui tam suits
  - -- Improper/constructive discharge claims
- State Attorneys General
  - -- State consumer protection and unfair competition statutes
  - -- Actions by one or more state AGs
  - -- AGs interested in off-label promotion, DTC advertising, fair balance, comparative/superiority claims
  - -- Compliance with FDA-approved labeling may not be enough
  - -- FDA review of promotional materials may not be enough
- State legislatures -- new California law requiring compliance with PhRMA Code and OIG Compliance Program

New Players -- Who Sets Federal Healthcare Policy? [cont'd]

- HHS OIG (FCA enforcement)
- Department of Justice (Anti-Kickback enforcement)
- FDA/DDMAC cooperation with the SEC, CMS, and FTC
- Product liability lawyers Competitors -- deceptive advertising/unfair competition litigation
- Shareholder liability suits -- Board misconduct/stock price manipulation
- Insurance carriers
  - -- Excluded coverage for foreseeable adverse events
  - -- Off-label promotion/foreseeable events not in labeling may negate learned intermediary defense

New Off-Label Issue

- Clinical trial databases
  - -- GSK settlement with AG Spitzer
  - -- Forest Labs settlement with AG Spitzer
  - -- Lilly/Merck clinical trial databases
  - -- PhRMA database (Oct. 2004) -- publicly available, free access database
    - -- Results of Phase III and IV clinical tests completed since October 2002
    - -- Published articles and unpublished study summaries
    - -- Sponsor's name
    - -- Name of drug/studied indications

New Off-Label Issue [cont'd]

- -- Link to FDA approved labeling
- -- Bibliography of published studies
- -- Database searchable by drug name, indication studied, study name, sponsor
- -- Ongoing clinical studies
  - -- Cancer -- 402
  - -- Heart disease/stroke -- 123
  - -- Neurological disease -- 178
- What will this mean for companies and their sales representatives?

Conducting An Off-Label Assessment

- Identify key products with potential or known off-label uses
- Review policies and procedures that address off-label uses
- Evaluate adequacy of existing training programs on off-label compliance issues
- Review relevant complaints to internal hotline or other internal reporting mechanisms
- Review recent FDA regulatory actions, whistleblower suits, judicial decisions, settlements
- Review complaints from competitors
- Assess effectiveness of compliance and audit programs

Special Areas for Review

- Off-label information -- who, when, how
- Promotional materials
- Instructions to and restrictions on sales representatives
- Role of medical liaisons
- Funding for medical education
- Marketing plans
- Compensation of sales representatives
- Interactions with physicians
- News releases
- Websites