The Basic Rules

- FDA approved labeling (the PI) is the regulatory point of reference
- Promotional materials must be consistent with the FDA-approved labeling
- Statements by, on behalf of, or funded by a pharmaceutical company may create an off-label use
What Kinds of Claims Can Be “Off-Label”?

- Unapproved use -- an indication not approved by FDA
- Broader indication than approved
- “Drug of first choice” claim
- Broader/different patient population
- Different dosage
- Different concomitant medications
- Unapproved comparative or superiority claims
- Claims based on preliminary/investigational data
- New outcomes -- pharmacoeconomic and quality of life claims
- Minimizing FDA-approved risk or safety information
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
- Dissemination of peer reviewed journal articles
- Medical education and “scientific exchange”

Dissemination of information about an unapproved use by or on behalf of a manufacturer can have consequences beyond FDA regulatory action
Scientific Exchange

■ The prohibition (21 CFR 312.7(a))

-- A company or someone acting on its behalf “shall not represent in a promotional context that an investigational drug is safe or effective for the purpose for which it is being investigated, or otherwise promote the drug”

-- However, the FDA prohibition “is not intended to restrict the full exchange of scientific information concerning the drug, including dissemination of scientific findings . . . “

-- Thus, the focus is on restricting promotional claims
CME/Scientific Exchange

- Company-funded CME
- Professional meetings
- Hospital and physician programs
- Professional and scientific publications
- Databases and registries
Where Does the First Amendment Come In?

- Drug promotion is commercial speech
- Regulation of commercial speech is 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 the speech substantial?
  - Does regulation of the speech directly advance the government’s interest?
  - Is the regulation more extensive than necessary to serve that interest?
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 promotion directly advances FDA’s interest

- Are FDA restrictions more extensive than necessary?
  -- The *Western States* case -- “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"
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
FDA Guideline on CME

- Companies can fund CME consistent with FDA guideline

- CME activities and materials not subject to FDA rules restricting off-label promotion and materials if companies adhere to FDA’s guidance

- FDA guidelines -- dissemination of off-label information within a CME program is acceptable if the program is independent and non-promotional

- Key element is independence -- CME content must be free of sponsoring company’s influence
FDA guideline identifies factors of independence

- Control over content and focus of program (single product)
- Disclosure of sponsorship
- Disclosure of speaker’s relationship to sponsoring company
- Speaker selection -- suggesting speakers actively involved promoting the sponsoring company’s products
- Scientific rigor and balance of the program
- Absence of promotional content
- Control over ancillary activities (sales/marketing) at the CME program and in the CME materials
- Opportunities for discussion
- Relationship between CME provider and sponsoring company
- Multiple presentations
-- Audience selection -- are invitation lists generated by sales/marketing department or do they reflect relationship-building efforts by the sponsoring company

-- Dissemination of CME materials after the program by sponsoring company

■ Impact of Washington Legal Foundation
  -- Safe Harbor regulations
  -- Enforcement discretion
PhRMA Code on Interactions with Healthcare Professionals -- Guidance on CME

- Companies may fund conferences through subsidies to conference organizers/providers
- Control over content, materials, and speakers resides with conference organizers/providers
- Company funding may include honoraria to faculty
- No financial support to non-faculty attendees but companies may provide scholarships to allow medical students, residents and interns to attend if selected by their academic institution
- Company funding may include meals and receptions if modest and if conducive to discussion by attendees
- CME means a conference or meeting primarily dedicated to promoting objective scientific and educational activities and discussion
Accreditation Council for Continuing Medical Education (ACCME) Guidelines

- CME provider decisions must be free of the control of the funding company (“commercial interest”)
  -- CME needs
  -- Educational objectives
  -- Selection and presentation of content
  -- Selection of educational methods
- A CME provider cannot be required to accept advice or services concerning teachers, authors or participants, or of content, from a funding company as a condition of funding
- Presentations must give a balanced view of therapeutic options
- Funding company may not pay for travel, lodging or honoraria of non-teacher participants

- Arrangements for commercial exhibits or advertising cannot interfere with the presentations and cannot be a condition of funding support

- No product promotion material or advertising in or during CME activities
Live or enduring promotional activities must be kept separate from CME

- No display or distribution of promotional materials in the educational space
- No promotional materials interleaved within the pages of CME content
- No “commercial breaks” in audio or video recording CME

Educational materials that are part of CME cannot contain any advertising or trade name message, but non-CME aspects of a CME activity can include product promotion materials and product-specific advertising
Presentations must disclose financial relationships of presenters to learners

Source of CME funding must be disclosed to learners; disclosure may not include trade name or product message

A written agreement documenting the terms of support
OIG Final Guidance -- Compliance Program Guidance for Pharmaceutical Manufacturers

- OIG focus is on anti-kickback implications of sponsorship of CME
- Under OIG guidance, companies should not use CME to channel improper remuneration to physicians in a position to generate business
- Compliance with the PhRMA Code will reduce risk of fraud and abuse but is not a safe harbor protecting a company from the anti-kickback laws
- OIG guidance also encourages compliance with FDA’s guidance
American Medical Association (AMA) CME Guidelines

- Sponsoring companies may provide subsidies to conference provider to reduce registration fees but may not give subsidies to individual physicians (speakers or attendees)
- Sponsoring companies may fund modest hospitalities -- meals/social events
- Sponsoring companies may fund scholarships so that students, residents and fellows may attend
- Physicians’ presentations should be scientifically accurate, balanced, not influenced by sponsor
- Physician presentations may present company-funded research and may use technical assistance from companies in preparing materials
- Physician presenter must disclose any conflicts of interest
Controlling CME Activity

- A written agreement with provider that makes clear that content will be independent, that the program will be educational and not promotional
- The agreement should require disclosure of support and any relationships between company and presenter
- Company may recommend presenters if acceptance of recommendations is not a condition of support
- Company may provide technical support (research data and materials) to presenter but not script presentation or direct presentation content
ISSUES

- Repeatedly supporting program by same provider
- Giving lists of potential invitees to provider
- Working with speakers
- Role of sales representatives in promoting CME
- Conduct of promotional activities in proximity of CME
- Subsequent use of CME materials
Risks and Implications of Off-Label Rules
Non-Compliance

- FDA non-compliance
- False Claims Act (Parke-Davis case causation theories)
- Anti-Kickback Act
- New players
  -- Whistleblowers
  -- State Attorneys General
  -- HHS OIG
  -- Department of Justice
  -- Product liability lawyers
  -- Competitors -- deceptive trade practice/unfair competition laws
  -- Shareholder liability suits
  -- Insurance issues
- FDA -- cooperation with SEC, CMS and FTC
Special Areas for Review In CME

- Off-label information/investigational data
- Funding for medical education/role of marketing
- Instructions to sales representatives participating in CME
- Marketing plans
- Relationships with CME providers
- Interactions with physicians
- Publicity about CME
- Websites
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 FD regulatory actions, whistleblower suits, judicial decisions, settlements
- Review complaints from competitors
- Assess effectiveness of compliance and audit programs