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MANAGING RISKS OF OFF-LABEL PROMOTION AND CONTINUING MEDICAL EDUCATION

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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 interleafed 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