Regulation of Drug Marketing

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FDLI

Key Principles of Advertising and Promotion

FDA Authority Under FDCA

- FDCA prohibits following relevant to drug marketing:
  - Causing a drug to be shipped into interstate commerce that is an unapproved new drug
  - Introducing into interstate commerce a drug that is misbranded

Intended Use

- Objective intent may “be shown by labeling claims, advertising matter, or oral or written statements”
- May be shown by circumstances where drug “is, with the knowledge of such persons or their representatives, offered and used for purpose for which it is neither labeled or advertised”

Intended Use and New Drug Approval

- FDCA prohibits introduction or delivery of new drug into interstate commerce without FDA approval
- “Intended use” is the objective intent of the person legally responsible for labeling of drug
- If drug promoted for intended use beyond approved indication, FDA may determine it is unapproved drug

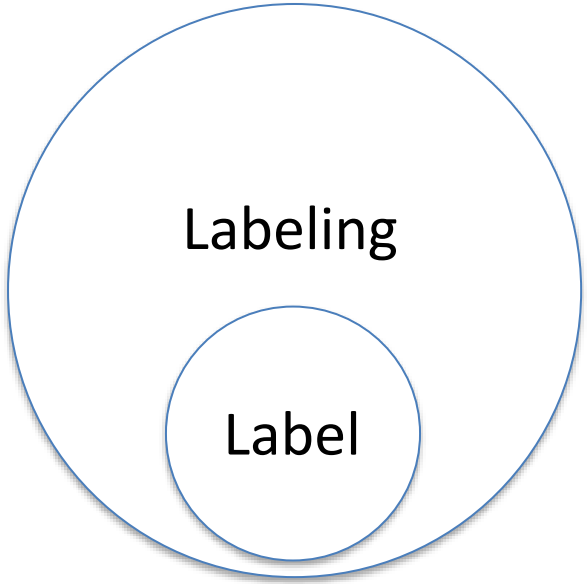
Misbranding

- FDCA holds manufacturers to a "high level of honesty" and an exacting measure of truthfulness
- Drug may be misbranded if:
  - Label or labeling is false or misleading "in any particular"
  - Inadequate directions of use
  - Material omissions
  - Inadequate directions or warnings
  - Lack of risk information

See FDCA § 502; 21 U.S.C. § 352

Statutory Definitions – The Federal Food, Drug, and Cosmetic Act (FDCA)

- Label = “a display of written, printed, or graphic matter **upon the immediate container** of any article . . .”
- Labeling = “all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article.”



Labeling

- Broad construction: “textual relationship to the drug”
- Does not need to be physically attached to the drug
- Labeling categories:
  - FDA-required labeling
  - Promotional labeling (any labeling, other than FDA-required labeling, for promotion of drug)

Office of Prescription Drug Promotion (OPDP)

- Responsible for regulation of advertising and promotional materials for prescription drugs within FDA
- All prescription drug promotional materials submitted to OPDP, but no requirement to seek pre-approval from OPDP in most cases
- Authority to issue an Untitled Letter or Warning Letter for noncompliance (latter generally requires corrective action)

Prescription Drug Promotion

Promotional Labeling vs. Advertisements

- Difference is distribution
- Advertisements not defined by FDCA; regulations provide examples (broadcast TV/radio or newspapers/magazines)
- Promotional labeling includes additional types of materials and ways to get them to the consumer

Promotional Activities

- Advertisements
- Brochures
- Booklets
- Mailing pieces
- Calendars
- Price lists
- Catalogs
- Letters
- Films
- Exhibits
- Literature
- Reprints

Non-Promotional Activity

- Scientific exchange
  - Specific responses to unsolicited requests for information (including requests for off-label information)
- Disease awareness communications
  - Intent to raise awareness of disease or condition
- Sponsorship of independent CMEs
  - Does company control who speaks? Content? Program focus? Audience selection?

Promotional Materials

- Must (among other things)
  - Include prominent mention of product's proprietary and established name
  - Be consistent with approved prescribing information (PI)
  - Contain a fair balance between drug's benefits and risks
  - Be truthful and non-misleading
  - Accompanied by required information (e.g., FDA-approved PI)

Fair Balance

- Requires companies to place sufficient emphasis on drug risks compared to drug effectiveness.
- FDA focus is on **net impression** – "whether the piece ***as a whole*** conveys an accurate and non-misleading impression of the benefits and risks of the promoted product."
  - Includes quantity, location, and order of information

Comparative Claims

- Claim related to relative efficacy and safety between drugs
- Must be supported by substantial evidence of safety and effectiveness from adequate and well-controlled investigations
  - 21 CFR § 202.1(e)(4), (6)(i)-(ii)

Pharmoeconomic Claims

- Claims that relate to the cost or economic value of a drug
- Requirements:
  - "Competent and reliable" scientific evidence;
  - Relate to drug's approved indication;
  - No representations about safety/efficacy;
  - Made to health care formularies or payors

Patient-Reported Outcomes

- Patient-reported outcome (PRO) instruments may be used to support claims in approved drug labeling
- PRO is any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else
- PRO instruments (i.e., a questionnaire plus the information and documentation that support its use) is a means to capture PRO data used to measure treatment benefit or risk in clinical trial

Patient-Reported Outcomes

- FDA guidance provides that review of a PRO instrument to support claims in medical product label includes the following:
  - Population enrolled in the clinical trial;
  - Clinical trail objectives and design
  - PRO instrument's conceptual framework;
  - PRO instrument's measurement properties

Internet / Social Media

- Generally, FDA has been unwilling to make exceptions for new media, although FDA has developed guidance for various online communications:
  - Internet/Social Media Platforms with Character Space Limitations Presenting Risk and Benefit Information for Prescription Drugs and Medical Devices – June 2014
  - Internet/Social Media Platforms: Correcting Independent Third-Party Misinformation About Prescription Drugs and Medical Devices – June 2014
  - Fulfilling Regulatory Requirements for Postmarketing Submissions of Interactive Promotional Media for Prescription Human and Animal Drugs and Biologics – January 2014
  - Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices – December 2011

Postmarketing Submission of Interactive Promotional Materials

- Guidance on interactive promotional media (e.g., blogs, social networking sites, podcasts)
  - FDA requires firms to submit "[a]t the time of the initial display . . . in its entirety all sites for which it is responsible," including interactive and real-time components on the sites.
  - Ongoing requirement to submit monthly list of relevant sites or screenshots of relevant content.

Character and Space Limitations

- Even on platforms with character and space limitations (e.g., Twitter, sponsored links), promotional material must still comply with FDCA:

  If an accurate and balanced presentation of both risks and benefits of a specific product is not possible within the constraints of the platform, then the firm should reconsider using that platform for the intended promotional message[.]

Correcting Third-Party Misinformation

- Per FDA guidance, misinformation is “positive or negative incorrect representations or implications about a firm’s product created or disseminated by independent third parties who are not under the firm’s control or influence”
- Firm has no obligation to correct third-party user generated content

Correcting Third-Party Misinformation

- How to correct:
  - Provide appropriate, truthful, and non-misleading corrective information, or
  - Provide a reputable source from which to obtain the correct information, such as the firm's contact information

Correcting Third-Party Misinformation

- Appropriate Corrective Information
  - Relevant and responsive
  - Limited and tailored
  - Non-promotional in nature, tone, and presentation
  - Accurate
  - Consistent with FDA-required labeling
  - Supported by sufficient evidence where needed
  - Posted in conjunction with or in reference to misinformation
  - Disclose the person providing the corrective information is affiliated with the firm.

Off-Label Information and Other Current Issues

First Amendment Issues / Off-Label

- Cannot promote false or misleading information and FDA cautions against proactive off-label promotion (but can disseminate peer-reviewed reprints)
- Can provide non-misleading responses to unsolicited requests for off-label information (if consistent with FDA guidance)
- First Amendment protections for truthful and non-misleading speech – highly contextual and evolving

Disease Awareness and "Help Seeking" Communications

- Intended to raise awareness of disease or condition, or in direct-to-consumer materials, encourage audience to seek more info/help
- FDA Guidance (2004) – communication should:
  - Discuss disease or condition
  - Not mention a particular product (express or implied)
  - If directed at consumers, advise consumers to "see your doctor" for diagnosis or treatment

Disease Awareness and "Help Seeking" Communications

- Can become promotional if:
  - Presented in combination with branded promotional materials
  - Use of promotional campaign elements (colors or graphics)
  - Company name in some circumstances (company is only manufacturer of drug for condition or company only manufactures one drug)

Pre-Approval Promotion

- Prohibited from representing investigational drugs are safe and effective for the purposes under investigation or otherwise promoting drug
  - 21 C.F.R. § 312.7
- Regulation “not intended to restrict the full exchange of scientific information concerning the drug, including dissemination of scientific findings in scientific or lay media”

Pre-Approval Promotion: Payor Communications

- FDA "does not intend to object" to the following types of information presented to payors if **unbiased, factual, accurate**, and **includes a clear statement that the drug is under investigation, the stage of product development, and that safety and efficacy have not been established**:
  - Product information (e.g., drug class)
  - Indication sought
  - Factual presentations from study results
  - Anticipated timeline
  - Product pricing information
  - Targeting/marketing strategies
  - Product-related programs or services

Scientific and Educational Activities

- Activities, supported by companies, that are otherwise independent from the promotional influence of the supporting company
  - Not labeling/advertising under FDCA
  - FDA “recognizes that industry-supported activities can be both nonpromotional and educational”

Scientific and Educational Activities

- FDA's 12-factor(!) test:
  - Control of content and selection of presenters/moderators
  - Disclosures
  - Program focus
  - Relationship between provider and supporting company
  - Provider involvement in sales or marketing
  - Provider's demonstrated failure to meet standards
  - Multiple presentations
  - Audience selection
  - Opportunities for discussion
  - Dissemination
  - Ancillary promotional activities
  - Complaints

Medical Science Liaisons

- Communicating safety information or updates, published papers, independent medical education, and responses for off-label information
- Must be consistent with FDA guidance on education and promotion
  - Should not promote off-label uses, make safety or efficacy claims about investigational drugs, or provide false or misleading information
  - Be wary of hybrid roles: title does not trump content where MSL assumes sales-like activities.

Good Reprint Practices

- FDA guidance (2009) provides manufacturers with principles to distribute medical and scientific information that discuss unapproved uses for drugs and medical devices
- Revised FDA guidance (2014) addresses distribution of scientific publications that contain off-label information about a drug
  - Reiterates principles from 2009 guidance
  - Expands scope to include distribution of reference texts and clinical practice guidelines (CPGs)

Good Reprint Practices

- Editorial Guidance
  - Should first have been published by an organization that has an editorial board that uses experts who have demonstrated expertise in the subject of the article under review by the organization
  - Experts should be independent of the organization and should review and objectively select, reject, or provide comments about proposed articles
  - Organization should adhere to a publicly stated policy of full disclosure of any conflict of interest or biases for all authors, contributors, or editors associated with the journal or organization

Good Reprint Practices

- Article/Distribution Guidance – Reprinted article should:
  - Be peer-reviewed and published in accordance with the peer-review procedures of the organization
  - Be unabridged reprint or copy of the article
  - Contain information that describes and addresses adequate and well-controlled clinical investigations that are considered scientifically sound by experts with scientific training and experience to evaluate the safety or effectiveness of the drug
  - Disseminated with approved labeling, and comprehensive bibliography and representative contrary publication (when possible)
  - Be separate from the delivery of promotional information

Good Reprint Practices

- Article/Distribution Guidance – Reprinted articles generally should not:
  - Be false or misleading
  - Contain information recommending or suggesting use of the drug makes the product dangerous when used in the manner suggested

Good Reprint Practices

- In addition, for unapproved uses, reprinted article should not:
  - Be in the form of a special supplement or publication that has been funded by the manufacturer of the drug
  - Be marked, highlighted, summarized, or characterized by the manufacturer to emphasize or promote an unapproved use
  - Be primarily distributed by a drug or device manufacturer
  - Be written, edited, excerpted, or published specifically for, or at the request of, a manufacturer
  - Be edited or significantly influenced by a manufacturer or any individuals having a financial relationship with the manufacturer
  - Be attached to specific product information (other than the approved product labeling or the product's cleared indications for use statement).

Good Reprint Practices

- Accompanying material – distributed article should include affixed statement disclosing:
  - The drug included in the journal reprint in which the manufacturer has an interest
  - That some or all uses of the manufacturer's drug described in the information have not been approved or cleared by FDA
  - Financial interests and affiliations of any author
  - Any person known to the manufacturer who has provided funding for the study
  - All significant risks or safety concerns associated with the unapproved use(s) of the manufacturer's product(s) discussed in the journal article that are known to the manufacturer but not discussed in the article

Good Reprint Practices

- Certain types of journal reprints are not consistent with FDA guidance:
  - Letters to the editor
  - Abstracts of a publication
  - Reports of healthy volunteer studies
  - Publications consisting of statements or conclusions but which contain little or no substantive discussion of the relevant investigation or data on which they are based

Communications with Payors, Formulary Committees, and Similar Entities

- Guidance addressing companies' communication of health care economic information (HCEI) to payors, formulary committees, and similar entities
- Audience includes
  - Public and private sector payors
  - Formulary committees (e.g., pharmacy and therapeutics committees)
  - Drug information centers
  - Technology assessment committees
  - Pharmacy benefit managers
  - Third party administrators

Communications with Payors, Formulary Committees, and Similar Entities

- HCEI is “any analysis (including the clinical data, inputs, clinical or other assumptions, methods, results, and other components underlying or comprising the analysis) that identifies, measures, or describes the economic consequences, which may be based on the separate or aggregated clinical consequences of the represented health outcomes, of the use of a drug.”

Communications with Payors, Formulary Committees, and Similar Entities

- Communications of HCEI to payors considered labeling if otherwise meets definition under FDCA.
- "Payors seek a range of information on effectiveness, safety, and cost-effectiveness of approved/cleared medical products, including information from firms, to help support their product selection, formulary management, and/or coverage and reimbursement decisions on a population basis."
  - Drug and Device Manufacturer Communications With Payors, Formulary Committees, and Similar Entities Questions and Answers Guidance for Industry and Review Staff (2018)
- FDA believes it is critical that information provided by companies to payors be (1) truthful and non-misleading and (2) that appropriate information be provided to enable payors to make informed decisions.

Communications with Payors, Formulary Committees, and Similar Entities

- FDA recognizes HCEI is presented in various ways:
  - Evidence dossier
  - Reprint of a publication from peer-reviewed journal
  - Software package comprising a model with a user manual
  - Budget-impact model
  - Slide presentation
  - Payor brochure

Communications That Are Consistent with FDA Required Labeling

- FDA guidance (2018) addressing companies' communications presenting information that is consistent with, but not contained in, the FDA-required labeling
  - "*Consistent with the FDA-required labeling* is limited to information about the approved or cleared uses of a product."

Communications That Are Consistent with FDA Required Labeling

- FDA applies three factors to determine whether communication consistent with required labeling:
  - Factor 1: How the information in the product communication compares to the information about those conditions of use in the FDA-required labeling regarding (1) indication, (2) patient population, (3) limitations and directions for handling/use, and (4) dosing or use regimen/administration.

Communications That Are Consistent with FDA Required Labeling

- Factor 2: Whether the representations/suggestions about the use of the product in the communication increase the potential for harm to health relative to the information reflected in the FDA-approved labeling.
- Factor 3: Whether the directions for use in the FDA-required labeling enable the product to be safely and effectively used under the conditions represented/suggested in the communication.

Communications That Are Consistent with FDA Required Labeling

- Example 1: Drug A and Drug B are both indicated for the treatment of osteoarthritis in dogs. Drug A's FDA-required labeling states that when discontinuing treatment with Drug A there should be a washout period before switching to another drug because of an increased risk of adverse reactions from drug interactions if dogs are switched without a washout period between the drugs. Drug B's FDA-required labeling does not address switching from Drug A to Drug B. A firm's product communication for Drug B suggests that dogs can be immediately switched from Drug A to Drug B.

Communications That Are Consistent with FDA Required Labeling

- **Factor 1** -- no information in the FDA-required labeling for Drug B that explicitly addresses use of Drug B in dogs being switched from Drug A
- **Factor 2** – information in the communication increases the potential for harm to health relative to the information in the FDA-required labeling for Drug B, which does not describe the additional risks associated with use of Drug B when dogs are abruptly switched to the drug from Drug A
- **Factor 3** – FDA-required labeling for Drug B would not provide adequate directions for use of Drug B under the conditions represented in the communication

Anti-Kickback Statute

- Prohibits knowingly and willfully soliciting or receiving (or offering or paying) any remuneration in return for (or to induce among other things, referrals for, or orders of, items or services reimbursable by a federal health care program.
  - 42 U.S.C. § 1320a-7b

False Claims Act

- Knowingly making or using, or causing to be used a false or fraudulent record or “material” to a false or fraudulent claim; or conspiring with others to commit such violations for payment or approval
- Whistleblower provisions permit private parties to bring suit o/b/o government and share in recovery
- Multi-million dollar settlements
- Note that many states have fraud and abuse statutes, including false claims, anti-kickback, and other statutes

OIG Compliance Program Guidance

- Office of Inspector General (OIG) compliance program guidance elements:
  - Implementing written policies and procedures
  - Designating a compliance officer and compliance committee
  - Conducting effective training and education
  - Developing effective lines of communication
  - Conducting internal monitoring and auditing
  - Enforcing standard through well-publicized disciplinary guidelines
  - Responding promptly to detected problems and undertaking corrective action

OIG Compliance Program Guidance

- Code of Conduct
  - "The code of conduct for a pharmaceutical manufacturer should articulate the company's expectations of commitment to compliance by management, employees, and agents, and should summarize the broad ethical and legal principles under which the company must operate."

OIG Compliance Program Guidance

- Three major potential risk areas for pharmaceutical manufacturers:
  - Integrity of data used by state and federal governments to establish payment
  - Kickbacks and other illegal remuneration
  - Compliance with laws regulating drug samples

Corporate Integrity Agreements

- Negotiated by OIG with manufacturers as part of settlement of federal health care program investigations
- Entities agree to obligations in exchange for OIG agreement not to seek their exclusion from participation in Medicare, Medicaid, or other federal health care programs

Corporate Integrity Agreements

- Typically lasts five years
- Various requirements (e.g., compliance officers, written policies, annual reports)
- Breach and default provisions permit OIG to impose monetary penalties for failure to comply with CIA (material breach basis to exclude entity from federal health care programs)