Regulation of Drug Marketing

Presented by:

Alan G. Minsk

Partner

Food and Drug Team

Arnall Golden Gregory LLP

alan.minsk@agg.com

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FDLI

Key Statutory Definitions
The Federal Food, Drug, and Cosmetic Act

- We won't go into too many details about the label and labeling requirements, as this is more for RA/QA personnel and there are product-specific considerations, but one should understand the basic reach of FDA's authority
- *Label* – "[A] display of written, printed, or graphic matter upon the immediate container of any article . . ."
- *Labeling* – "[A]ll labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article"
- Advertising, not specifically defined in the law; FDA's implementing regulations offer examples – we typically think of direct-to-consumer
- Our focus will be on FDA and the FDC Act

Scientific Exchange vs. Promotion

My Thoughts

- Education vs. spin
- Context and perception
  - solicited vs. unsolicited request
  - marketing vs. medical affairs
  - greatest hits vs. entire reprint
- Relevance is the level of FDA regulation and oversight

Non-Promotional Information

Some Examples

- Specific responses to unsolicited requests for information
  - FDA has not regulated and does not intend to regulate industry-supported scientific and educational activities that are independent of the influence of the supporting company
  - the key is whether the Continuing Medical Education (CME) activities are free from the supporting company's influence and bias
- Disease-awareness communications
- CME-type activities

Disease State and Help Seeking Ads

- Disease state and help seeking (e.g., see your doctor) communications do not mention product-specific information
- Therefore, such communications do not require compliance with fair balance requirements

Labeling

- Labeling may include:
  - instructions for use, posters, tags, pamphlets, circulars, booklets, brochures, instruction books, direction sheets, websites, and other promotional materials, external training materials or manuals
- Make sure standard operating procedures reflect these areas
  - the reach of the term “labeling” is broad, because it extends beyond mere physical association with the product

Labeling *(cont'd)*

- However, the reach is not unrestricted
  - it must function as labeling
    - i.e., it must supplement or explain a product to help in the product's use
      - disease state communications, without product reference, and Continuing Medical Education activities are typically not considered labeling
  - it must be supplied or disseminated by or on behalf of the manufacturer, packer or distributor
    - it's a control issue
- Everyone acting on behalf of the company is held to the same standards as the company and the company will be held responsible, even if the agent fails to conform to company policies
  - e.g., investigators, consultants, PR firms, marketing partners

Did It Make It Into The Label?

- Final FDA-approved label controls the scope of post-market activities
  - indication(s)
  - population
  - efficacy
  - comparative claims
- If not included in the label, consider whether the exclusion was intentional
  - e.g., FDA did not consider the data at all or it did and rejected the data's inclusion

Prescription Drug Advertising

- Must show (among other things)
  - the drug's "established name shall be in printed letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined . . ."
  - truthful and non-misleading brief summary relating to benefits and risks (to be discussed)
  - fair balance of risks and benefits (to be discussed)
  - for Rx drug broadcast ads, the product's most important risk-related information in the audio/visual parts of the ad ("the major statement") and either a brief summary of the advertised product's risk information or a place to look for more information ("adequate provision")
    - ❑ e.g., 1-800 number, website, "See Your Doctor," "See our ad in _____"

What Is “Fair Balance”?

- Balance between information relating to side effects, contraindications, warnings and precautions and information related to effectiveness
  - Contextual Fair Balance
    - ❑ comparable scope, depth and detail
  - Physical Fair Balance
    - ❑ reasonably comparable prominence and readability, taking into account, for example, typography, layout, contrast, headlines, paragraphing and white space

Brief Summary

- With limited exception, prescription drug advertisements must include a true statement of information in brief summary relating to side effects, contraindications, and effectiveness
- A brief summary is not needed for certain types of advertising (e.g., reminder ads, help-seeking ads)
  - but cannot have reminder ads or labeling for Black Box Warning products

Words Are Very Unnecessary

- Verbal statements that are not “labeling” can change a product’s intended use
  - e.g., trade show statements, workshops, seminars, hands-on demonstrations
- The intended use is what the product does
- Based on the objective intent of persons legally responsible for labeling
- Determined by expressions or circumstances surrounding distribution of product

Cost Comparisons/Pharmacoeconomics

- FDA does not prohibit cost analyses or cost comparisons
- Should perform clinical studies to demonstrate cost effectiveness
- Be careful about false or misleading comparisons – should be presented honestly and accurately
  - ensure relevance
  - Don’t overstate cost in relation to safety and effectiveness
  - actual costs should be conveyed
    - no hidden costs
- Information allowed to certain entities

Some Related Areas in Social Media to Consider

- Search engine ads
- YouTube videos
- “Facebook Share” widget
- URL address
- Banner ads
- Webinars and webcasts
- E-messaging
- Apps
- Blogs, chat rooms
- Unbranded websites
- Twitter
- Ads on social media sites (e.g., YouTube, Facebook)
- Clinical trial recruitment

Bottom Line

“Our laws for how products that are approved by the agency can be marketed to consumers are the same regardless of the medium, whether they are print ads, radio ads, television ads or internet ads.”

-- *Quote from an FDA official*

“If the information source is your own, such as your Facebook page or blog, then you have an obligation to police those because they’re yours.”

-- *Quote from an FDA Official*

Patient-Reported Outcomes

- Patient reported outcome (PRO) instruments can be used to support claims in approved medical product labeling
- A PRO instrument (i.e., a questionnaire and the information and documentation that support its use) may capture PRO data used to measure treatment benefit
- A 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
- The outcome can be measured in absolute terms (e.g., severity of a symptom, sign, or state of a disease) or as a change from a previous measure

Patient-Reported Outcomes *(cont'd)*

- The evaluation of a PRO instrument to support claims in medical product labeling includes the following considerations:
  - the population enrolled in a clinical trial
  - the clinical trial objectives and design
  - the PRO instrument's conceptual framework
  - the PRO instrument's measurement properties

Comparative Claims

- While comparative claims are not illegal, FDA discourages the practice and has indicated that frequently such comparisons are incomplete and can be misleading
  - must be based on reliable and sound scientific data
  - should be a head-to-head testing with the competitive product in a well-controlled trial to support claim
- If a study compares two products, FDA recommends that it be presented in its entirety and must identify where the product could also be inferior, if applicable
  - minimize misbranding or unapproved product challenge

Comparative Claims *(cont'd)*

- Make sure it's a valid apples-to-apples comparison, for example:
  - claims are the same
  - populations/users are the same
  - correct information in context
  - substantiating data
    - multiple corroborating sources are preferable
  - if there are distinctions, note them
- The government may take enforcement action against companies that make comparative claims that promote an off-label use or offer a misleading statement about a competing product

Over-the-Counter Drug Advertising

- The Federal Trade Commission regulates OTC drug advertising – the standards are substantiation, truthful, and fairness
- FDA regulates OTC drug labeling

Misbranding

- See 21 U.S.C. § 352 (or also known as section 502 of the FDC Act)
- Among other things:
  - the label or labeling is false or misleading “in any particular”
  - material omissions
  - inadequate directions for use
  - inadequate warnings
  - lack of risk information
- In short, not telling a complete, truthful story

Misbranding *(cont'd)*

- Ambiguity, misdirection, false comparisons to other products, and creating a false impression (including icons, symbols, URLs) are also ways to misbrand a product
  - every picture tells a story
- Some buzzwords that might raise FDA scrutiny (although not necessarily illegal)
  - all
  - none
  - more than
  - better
  - never
  - best
  - most
  - "er"-ending comparisons
  - "safe" and "effective" for an investigational product
  - unique

Medical Science Liaisons

- Separate from field sales activities
  - focus is on, for example, discussing clinical research ideas, reviewing new disease concepts, responding to off-label requests for information
- Activities must be consistent with FDA guidelines regarding education and promotion
  - e.g., MSLs cannot promote off-label uses, suggest an investigational product is safe and effective, or provide false or misleading information
  - MSLs should not and cannot become de facto sales reps
  - anything that is shared externally should be reviewed internally to ensure regulatory compliance
  - FDA is more concerned about the content of the company's presentation of information than the title of the person providing the content

Office of Prescription Drug Promotion

- The agency that reviews promotional materials for compliance
- For most prescription drug products, there is no requirement to seek approval from OPDP, but a company must submit materials on a Form 2253 at the time of initial publication or dissemination
- OPDP can issue an Untitled Letter or Warning Letter for noncompliance
  - most Warning Letters require corrective action

Off-Label Dissemination

- Cannot promote false or misleading information and FDA cautions against proactive off-label promotion (but can disseminate peer-reviewed reprints)
- Cannot solicit for an unsolicited request for off-label information
- Can respond to a truly unsolicited, specific request for off-label information
- First Amendment challenges – “truthful, not misleading” seems to be the evolving standard

Good Reprint Practices Guidance

- Draft guidance entitled “Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices”
- The draft guidance provides manufacturers with guidelines regarding the dissemination of peer-reviewed scientific journal articles regarding unapproved uses of drugs or medical devices
- Under the draft guidance, the article of reference must be published by an organization that has an editorial board consisting of experts in the subject area of the article

Good Reprint Practices Guidance *(cont'd)*

- The organization should adhere to a policy of full disclosure of any conflict of interest or bias of any author, contributor, or editor associated with the article
- The article must be peer-reviewed and published in accordance with sound scientific principles
- The draft guidance also prohibits the distribution of special supplements or publications that have been funded by one or more of the manufacturers of a product mentioned in the publication

Good Reprint Practices Guidance *(cont'd)*

- The information contained in such publications must address adequate and well-controlled clinical investigations that are considered scientifically sound by experts with sufficient training to evaluate the safety or effectiveness of the drug or device
- The information cannot be false or misleading, such as an article or reference text that is inconsistent with the weight of credible evidence derived from adequate and well-controlled clinical studies
- If the conclusion of the article or text has been specifically called into question by another article, the material must be distributed with the article that reached the contrary conclusion

Good Reprint Practices Guidance *(cont'd)*

- Drug and medical device manufacturers may distribute unabridged reprints of peer-reviewed research from reputable medical journals so long as:
  - the articles were not written, edited, or published specifically for, or at the request of, a drug or device manufacturer;
  - the publication has not been edited or otherwise "significantly influenced" by a drug or device manufacturer or any individuals with a financial relationship to the company;
  - the scientific information is distributed in an unabridged reprint or copy without any markings, highlighting, or characterization of the information;

Good Reprint Practices Guidance *(cont'd)*

  - the reprint is accompanied by a comprehensive bibliography of publications discussing adequate and well-controlled clinical studies published in a medical journal or scientific text about the product covered by the information disseminated;
  - no other promotional materials are attached to the reprints; and
  - the reprint is labeled as describing uses that have not been approved by the FDA for the product and is accompanied by the product's approved labeling

- The draft guidance does not apply to the following publications: (1) letters to the editors; (2) abstracts of a publication; (3) reports of Phase 1 clinical trials; or (4) reference publications that contain little or no substantive discussion of the relevant investigation

Communications that are Consistent with the FDA Required Labeling (FDA Guidance)

Scope

- Addresses communication of information that is consistent with, but may not be expressly included in, the FDA-required labeling for medical products
- To be consistent with the required labeling, communications must satisfy three factors:
  - Factor 1: How the information in the communication compares to the information about the conditions of use in the required labeling, focusing on the following areas to evaluate whether they are different from the FDA-required labeling: (1) indication, (2) patient population, (3) limitations and directions for handling/use, and (4) dosing/administration

Communications that are Consistent with the FDA Required Labeling (FDA Guidance) *(cont'd)*

- Factor 2: Whether the representations or suggestions increase the potential for harm to health when compared to the FDA-required labeling

  - e.g., a drug is reserved for third-line use because of safety issues; if communications about the drug state or imply that all patients should try the product (without determining if first or second-line therapies are suitable), the communication would not be consistent with the safety profile approved by FDA

- Factor 3: Whether the directions for use in the FDA-required labeling allow the product to be safety and effectively used as described in the communication; if not, the communication is not consistent

Communications that are Consistent with the FDA Required Labeling (FDA Guidance) *(cont'd)*

- Communication must not false or misleading
  - representations or suggestions must be grounded in science and presented with appropriate context
  - communication should include the limitations of the evidence
  - but, if the communication relies on an inadequate study, even including those limitations, the communication may be considered misleading

Communications with Payors, Formulary Committees, and Similar Entities (FDA Guidance)

- This guidance addresses how companies can communicate information on the effectiveness, safety, and cost-effectiveness of their approved or cleared medical products with entities making product selection, formulary management, and coverage and reimbursement decisions
- FDA recognizes that these entities may request information that differs from, or is in addition to, the information the agency reviews
- Because these payor decisions affect a large patient population, FDA "believes it is critical that HCEI [healthcare economic information] provided by firms to payors about their approved drugs and approved/cleared devices be truthful and non-misleading"

Communications with Payors, Formulary Committees, and Similar Entities (FDA Guidance) *(cont'd.)*

- The guidance adds slide presentations and payor brochures as examples to the list of types of communications through which a company may present HCEI
- The guidance notes that payors include both public and private sector entities, as well as third-party administrators
- FDA confirms that HCEI is considered promotion and, thus, is subject to the requirements for submission of promotional materials (e.g., submitting such materials to FDA at the time of initial publication or dissemination on a Form FDA 2253)

One Thing Leads to Another

- FTC or DOJ enforcement
- Corrective advertising
- Loss of credibility with FDA and the marketplace
  - e.g., consumers, medical community
- Competitors will use it against you
  - e.g., trade complaint, Lanham Act lawsuit, National Advertising Division challenge
- Individual liability - prosecution
- Bad publicity

One Thing Leads to Another *(cont'd)*

- Whistleblower complaints
- Product liability (evolving preemption doctrine)
- State prosecution
  - e.g., consumer deception
- Punitive damages
  - varies by state – might have state claim of consumer deception
  - compliance with FDA labeling requirements may bar recovery
  - no private cause of action under the FDC Act, but not a per se defense
- Diversion of $ from other projects to correct violative message

Off-label Reimbursement Implications

- False Claims Act Enforcement
  - 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
- Multi-million dollar settlements
- Corporate Integrity Agreements
- Potential criminal prosecution
- These are separate from FDA prosecution

OIG Compliance Program Guidance For Pharmaceutical Manufacturers

- The OIG identifies three major potential risk areas for pharmaceutical manufacturers:
  - kickbacks and other illegal remuneration
  - compliance with laws concerning drug samples
  - integrity of data used by state and federal governments to establish payment
  - Many states require companies to have corporate compliance programs

The Sunshine Act

- Calls for reporting to a publicly-available database information regarding transfers of value from industry to physicians and teaching hospitals, as well as ownership of industry by physicians
- Applies to companies with at least one approved/cleared product