Regulation And Dissemination Of Off-Label Information

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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

• Disease awareness communications
• CME-type activities
• Specific responses to unsolicited requests for information
Good Reprint Practices Guidance

• FDA recently finalized and released its guidance document, “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”

• FDA intends the guidance to provide manufacturers with guidelines regarding the dissemination of peer-reviewed scientific journal articles regarding unapproved uses of drugs or medical devices
Good Reprint Practices Guidance

(cont’d)

- Some focus points include independence, peer-reviewed and truthful information, full disclosure of potential relationships with the authors and regulatory status of mentioned product, education (versus promotion), and scientifically sound data
Good Reprint Practices Guidance (cont’d)

- The guidance does not apply to the following publications, which are not considered scientifically sound:
  - ✅ letters to the editors
  - ✅ abstracts of a publication
  - ✅ reports of Phase 1 clinical trials
  - ✅ reference publications that contain little or no substantive discussion of the relevant investigation

- We have prepared a Bulletin on the guidance if you would like a copy
Medical Science Liaisons

• Typically, field-based scientists provide scientific information to the healthcare community, particularly key thought leaders

• Separate from field sales activities

• Activities must be consistent with FDA guidelines regarding education, advertising and promotion
Medical Science Liaisons
(cont’d)

• MSLs cannot promote unlawfully
  ✓ no proactive off-label promotion
  ✓ no promotion or commercialization of an investigational product as safe, effective or approved
  ✓ no false or misleading information
Medical Science Liaisons
(cont’d)

• FDA is more concerned about the content of the company’s presentation of information than the title of the person providing the content

• Consider training programs for MSLs, separate from sales, to focus on the science of the disease states and products
Solicited Versus Unsolicited

- Solicited – prompting or encouraging the healthcare professional to ask a question
  - “would you like more information about Product X?”
  - a button with “Ask me about Product X”
  - placing a brochure in a trade show booth about off-label information

- Unsolicited – the healthcare professional initiates the conversation
Solicited Versus Unsolicited (cont’d)

- Can discuss approved uses
- If off-label and unsolicited, can respond but still be careful about liability implications
  - consider punting to Medical Affairs in the home office or to a Medical Information General Call Desk to have that group disseminate the information and include approved package insert
Approved Materials

• Medical liaisons should only use company-approved materials (even if they aren’t leaving them behind) obtained from literature services

  ✓ no unapproved materials

  ✓ no homemade materials

  ➢ includes highlighting an article or spinning the information
Approved Materials
(cont’d)

• Regulatory should review, with medical affairs, materials to assess, among other things:
  ✓ accuracy and appropriateness of information
  ✓ fair balance of information and regulatory compliance
  ✓ the materials are educational rather than promotional in tone
**Misbranding**

- **See** 21 U.S.C. § 352 (or also known as section 502 of the FDC Act)

- Among other things:
  - ✓ label or labeling is false or misleading in any particular
  - ✓ inadequate directions for use
  - ✓ inadequate warnings
  - ✓ lack of risk information

* An unapproved new drug is a separate violation*
Misbranding
(cont’d)

- Keep in mind that icons, symbols, website addresses, and other forms of communication can misbrand a product.
- Failure to provide material information is unlawful.
- “False or misleading” is not confined to meaning “untrue, forged, fraudulent or deceptive.”
- Ambiguity, misdirection, false comparisons to other products, and creating a false impression are also ways to misbrand a product.
FDA Enforcement Options

- Untitled Letter/Notice of Violation
- Warning Letter
- Injunction
- Seizure
- Criminal action
- Fines
Untitled Letter Or Warning Letter

• Typical result for violative promotional claim

• Source of violations
  ✓ competitor complaints (majority)
  ✓ FDA monitoring
    ➢ e.g., review of periodicals, attendance at trade shows, websites, Form FDA-2253
      ▪ i.e., Form FDA-2253 is submitted to FDA when a promotional piece is initially disseminated or initially published
Untitled Letter Or Warning Letter
(cont’d)

- inspections (of manufacturing facilities)
- complaints
- other agencies
  - e.g., FTC, SEC
Untitled Letter Or Warning Letter

(cont’d)

• Where FDA looks:
  - ✓ company website
  - ✓ brochures
  - ✓ instruction manuals
  - ✓ promotional flyers
  - ✓ bulk mailings
  - ✓ videotape
  - ✓ advertisements in journals
  - ✓ press releases
  - ✓ newsletters
Some Key Takeaways From FDA Enforcement

- The agency has maintained (and the courts have upheld elsewhere) that false speech is not protected commercial speech.
- Direct-to-consumer promotion is of particular concern to FDA.
- Promotions that are highly visible increase risk.
  - e.g., national medical conference, TV.
Some Key Takeaways From FDA Enforcement (cont’d)

• Promotions that raise safety concerns are likely to trigger FDA action

• Verbal statements can be violative, so it’s important to watch what your company employees or agents say, particularly at trade shows and medical conferences
Other Possible Implications

- Corrective advertising
- Loss of credibility with FDA and the marketplace
  - e.g., consumers, medical community
- Stock drop/class action lawsuits/SEC inquiry
- Competitors will use it against you
  - e.g., trade complaint letter, Lanham Act lawsuit, National Advertising Division challenge
Other Possible Implications
(cont’d)

- Bad publicity
- Whistleblower complaints
- Product liability
- State prosecution
- Fraud prosecution and abuse

✓ e.g., False Claims Act

- Diversion of $ from other projects
- Reputation in the medical and patient communities
- Other regulatory agencies

✓ e.g., SEC
Keep In Mind

- 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

  ➢ Warning Letter to drug company (2007)

    - Speaker/doctor gave presentation which contained off-label information to Maryland Department of Health and Mental Hygiene’s Pharmacy and Therapeutics Committee on behalf of company
Recommendations

• Comply with FDA’s labeling and promotional requirements, such as
  ✓ required product information
  ✓ truthful presentation of data
  ✓ fair balance
Recommendations (cont’d)

• Establish procedures before distribution and a team to review all promotional materials, regardless of the intended audience or the form of the promotion
  
  ✓ e.g., an internal review checklist that requires signoff by appropriate personnel
  
  ✓ Make clear in training and in SOPs the roles of individuals, the laws, government guidances, and company policies

• No handmade materials should be prepared and distributed
Recommendations (cont’d)

• Make clear what’s “approved” and what’s “investigational”

• Carefully consider the claims you want to put in the label and which you can demonstrate
  ✓ this is the labeling FDA will review

• If FDA rejects a claim, you would be ill advised to promote that claim anyway

• Be careful about symbols, logos, URL addresses, or graphics that can also get a company into trouble with intended use issues
Recommendations (cont’d)

- Remain vigilant in monitoring promotional activities
- Disclaimers or qualifying statements are helpful but won’t eliminate risk if the whole promotion, when viewed in full and in context, is violative
  - “this [disclaimer] statement does not mitigate the misleading impression conveyed” (sample FDA enforcement language)
- No ghostwriting
Recommendations
(cont’d)

• Do not get hung up with titles, such as MSLs
  ✓ FDA is more concerned about content and message

• Be careful at trade shows and educational conferences, because FDA officials and competitors like to attend these
  ✓ be careful of verbal statements
Recommendations (cont’d)

• Be aware of your marketing partner’s promotional activities relating to your product and what FDA has done, if anything, to company competitors

• Ensure review by company’s foreign and domestic regulatory department (e.g., foreign marketing practices), where marketing piece is generated by foreign entity for U.S. publication
Recommendations (cont’d)

• Train employees and third parties you employ about company policies
  ✓ you don’t want renegade salespeople getting the company in trouble

• Audit and monitor internally to make sure everyone is on the same page
  ✓ document accordingly

• The OIG has made several recommendations concerning auditing and monitoring (not discussed here)
False Claims Act

- The FCA prohibits knowingly making or using (or causing to be made or used) a false record or statement to get a false or fraudulent claim paid or approved by the federal government or its agents.
- Medicaid will not reimburse for off-label prescriptions unless the drug and use are in an official compendium.

We won’t discuss here the anti-kickback statute.
False Claims Act
(cont’d)

• U.S. can sue to recover improperly paid monies, together with civil penalties, under the FCA

• Whistleblowers can sue on behalf of the government (qui tam proceeding)
  ✓ if successful, they can receive a percentage of recovery
Penalties For Non-Compliance

OIG or U.S. Attorney

- Criminal and/or civil penalties
- Exclusion from participation in federally funded healthcare programs
  - e.g., Medicare or Medicaid will not reimburse for the product
- Penalties can apply to the company, healthcare professional recipient, and distributors that do not directly bill federal healthcare programs
### Some Enforcement Examples Relating To Off-Label Promotion

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<td>$34.7 mil.</td>
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Important Points To Consider With Enforcement Examples

• Some of the uses promoted were reviewed and **not** approved by FDA

• Distribution of journal article reprints to further an alleged off-label promotional campaign

• Scrutiny into physician payment disclosure, such as preceptorships

• Companies allegedly promoted uses that could cause patient harm
Considerations

• Determine whether the company has liability exposure
• Either develop policies and procedures designed to address potential exposure or amend existing policies to address weaknesses and areas of undue exposure
  ✓ have state-of-the-art compliance programs designed to detect and root out illegal practices and have an open-door policy to hear internal concerns
• Train and retrain employees, including management
Freebie

- We’ve written articles about promotional-related issues. If you’d like a courtesy copy, please give me your card or email me at alan.minsk@agg.com