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# Understanding the Parameters of Conversation and Dissemination of Off-Label Use Information

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Tweeting about this conference?
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# Agenda

- Regulatory Chronology
- Practical Tips
- Best Practices
  - Updated Training for Sales Force
  - Issues Related to Use of Contract Sales Force
  - Balancing Sales and Practice of Medicine
  - Consideration of FCA Exposure
- Expectations for Future Guidance

# Regulatory Chronology

- Parameters for Promotion
  - Guidance Documents
    - 1997 – Industry-Supported Scientific and Educational Activities
    - 2004 – "Help-Seeking" and Other Disease Awareness Communications by or on Behalf of Drug and Device Firms
    - 2011 – Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices
    - June 2014 – Internet/Social Medial Platforms with Character Space Limitations – Presenting Risk and Benefit Information for Prescription Drugs and Medical Devices
  - Trade association codes of conduct
  - Government settlements

# Regulatory Chronology

- FDA's approval process lags behind the pace of medical discovery
  - Doctors often depart from FDA's approved labeling
    - FDA is not authorized to interfere with the practice of medicine
  - Frequently, off-label use is the "standard of care"
    - Examples: oncology and psychiatry fields
- FDA recognizes the public health and policy justification supporting dissemination of truthful and non-misleading information.
  - "The public health may be advanced by healthcare professionals' receipt of medical journal articles and medical or scientific reference publications on unapproved new uses of approved or cleared medical products that are truthful and not misleading."

# Regulatory Chronology

- 1996:
  - FDA finalized two guidance documents. 61 Fed. Reg. 52800 (Oct. 8, 1996).
    - Guidance to Industry on Dissemination of Reprints of Certain Published, Original Data.
    - Guidance for Industry Funded Dissemination of Reference Texts
- 1997:
  - Congress added a safe harbor for dissemination of written materials.
    - FDAMA Section 401: Described conditions under which a drug or device manufacturer could disseminate written materials discussing a new use of its product.
    - If conditions were met, the government may not use the dissemination as evidence of the manufacturer's intent to create a new intended use. (21 U.S.C. § 360aaa-6(b).

# Regulatory Chronology

- 1998 and 1999:
  - First Amendment challenge to FDAMA § 401 and guidance documents
    - District court enjoined FDA from "in any way . . . limit[ing] any pharmaceutical or medical device manufacturer" from disseminating journal articles or medical texts, among other things.
      - *Washington Legal Foundation v. Henney*, 56 F. Supp. 2d 81 (D.D.C. 1999); *Washington Legal Foundation v. Friedman*, 36 F. Supp. 2d 16 (D.D.C. 1999); Washington Legal Foundation v. Friedman , 13 F. Supp. 2d 51 (D.D.C. 1998).
- 2000:
  - The DC Circuit Court of Appeals vacated the district court's decisions.
    - FDAMA and its implementing regulations constitute a ''safe harbor'' for a manufacturer that complies with them before and while disseminating journal articles and reference texts about ''new uses'' of approved products.
    - If a manufacturer does not comply, FDA may bring an enforcement action under the FDCA, and seek to use journal articles and reference texts disseminated by the manufacturer as evidence that an approved product is intended for a ''new use.''
      - *Washington Legal Foundation v. Henney*, 202 F.3d 331 (D.C. Cir. 2000).
- Sept. 30, 2006:
  - Sunset of FDAMA § 401 and its implementing regulations at 21 C.F.R. Part 99

# Regulatory Chronology

- 2009:
  - In light of the statute's sunset, FDA issued new guidance: "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."
    - Similar elements as contained in FDAMA § 401.
    - Caveat: "However, if a manufacturer engages in other conduct that unlawfully promotes an unapproved use of a medical product – whether or not the manufacturer also engages in conduct in conformance with the recommendation in this guidance – such other conduct may result in enforcement action."

# Regulatory Chronology

- Feb. 2014:
  - FDA issued a revised draft guidance on this issue: "Revised Draft Guidance for Industry on Distributing Scientific and Medical Publications on Unapproved New Uses – Recommended Practices."
    - Based on comments received on the 2009 guidance requesting clarification of how it applies to medical textbooks, and two citizen petitions filed by industry concerning, among other things, Clinical Practice Guidelines (CPGs).
    - 158 comments received
- June 2014:
  - FDA issued a distinct guidance on the dissemination of safety information related to approved uses of a drug: "Distributing Scientific and Medical Publications on Risk Information for Approved Prescription Drugs and Biological Products – Recommended Practices."
    - Based on comments received on Draft Reprints Guidance.
    - "FDA recognizes that the safety profile of a drug evolves throughout its lifecycle as the extent of exposure to the product increases . . . . FDA anticipates that the earliest distribution of new risk information will generally involve distribution of recently published studies, as opposed to textbooks or clinical practice guidelines."
    - Does not govern medical devices.

# Draft Reprints Guidance

- Includes most of the principles contained in the 2009 Guidance.
  - FDA emphasizes that all distributed materials should not:
    - Be false or otherwise misleading;
    - Recommend or suggest use of the product in such a way that the product is dangerous to health when used in the manner suggested; nor
    - Be marked, highlighted, summarized, or characterized by the manufacturer, in writing or orally, to emphasize or promote an unapproved use.
- Adds sections for reference texts and CPGs.
  - These publications are generally longer and cover a wider range of topics than a journal article.

# Draft Reprints Guidance

- Reference Texts must:
  - Be based on a systematic review of the existing evidence;
  - Be independently published;
  - Be the most current version;
  - Be written by experts in the subject area;
  - Be peer-reviewed by other subject area experts;
  - Be widely available through normal independent distribution channels;
  - Not be distributed with any product promotional materials;
  - Include a permanently affixed, and prominently displayed statement disclosing (1) the distributing manufacturer, (2) that some of the uses described in the text may be unapproved or not cleared by FDA; and (3) whether any specific authors have a financial interest in the manufacturer or its products; and
  - If there are one or more chapters that primarily discuss unapproved or uncleared uses, be accompanied by the approved product label (or indications of use for a 510(k) cleared device).

# Draft Reprints Guidance

- If only part of a reference text is distributed, the guidance requires that:
  - The overall reference text meets the requirements above;
  - The permanently affixed, prominently displayed statement is placed on the distributed part of the reference;
  - The affixed statement includes all known significant risks associated with the unapproved or uncleared use;
  - The distributed part of the reference text be unaltered, unabridged, and extracted directly from the original referent text; and
  - It be distributed with a copy of the approved product label (or indications of use for a 510(k) cleared device).

# Draft Reprints Guidance

- Clinical Practice Guidelines
  - CPGs are recommendations to help clinicians made decisions for individual patient care, and are generally longer and cover a wider range of topics than a journal article.
  - The Draft Guidance imposes Institute of Medicine (IOM) standards for determining whether it is "trustworthy":
    - Is based on a systematic review of the existing evidence;
    - Is developed by experts in the subject area;
    - Considers important patient subgroups and patient preferences;
    - Is transparently developed and funded such that biases are minimized;
    - Provides logical relationships between treatment recommendations, health outcomes, and includes the quality and strength of the underlying evidence; and
    - Is reconsidered and revised as new information becomes available.
  - Similar to reference texts, FDA lays out several requirements for CPGs that are distributed in their entirety, and additional requirements if only a section is used.

# Practical Tips

- Establish written procedures tailored to the Draft Guidance.
  - Define clear responsibilities for all relevant personnel (e.g., sales rep, marketing department, regulatory).
  - Institute Reprint Review Boards, so there is consistency in determining whether information meets the criteria in the Guidance
    - E.g., peer-reviewed, unabridged, scientifically sound, conflict of interest, disclosures.
  - Train all relevant personnel regularly
    - Make part of annual sales meetings

# Practical Tips

- Maintain an updated bibliography of all information related to your medical product.
  - Guidance requires that a reprint be disseminated with a comprehensive bibliography of publications discussing adequate and well-controlled studies about the use of the product covered by the information disseminated.
  - Will help update and identify the “representative publication” that reaches contrary conclusions regarding the unapproved use.

# Practical Tips

- Require documentation of compliance
  - The Draft Reprints Guidance does not require the company to maintain detailed records, but it could provide good evidence to defend the company if challenged.
  - But the guidance document on responding to unsolicited requests for information requires the firm to maintain records of:
    - The nature of the request for information, including the name, address, and affiliation of the requestor
    - Records regarding the information provided to the requestor
    - Any follow-up inquiries or questions from the requestor

# Practical Tips

- Continue segregation of medical team and sales team
  - Guidance requires that scientific and medical information be distributed separately from information that is promotional in nature.
    - Make explicit when discussion, whether in doctor's office or at medical conference, is scientific exchange or promotional.
    - Use segregated booths at exhibit halls – reserved for physicians to respond to attendees' requests for medical information.

# Practical Tips

- Seek FDA premarket review
  - If data are truthful and non-misleading, they support the safety and efficacy of the product.
  - "Although this draft guidance, like the 2009 guidance, recognizes the value to health care professionals of truthful and non-misleading scientific or medical publications on unapproved new uses, ***it also continues to recognize that this information is no no way a substitute for the FDA premarket review process, which allows FDA to be proactive, rather than reactive, in protecting the public from unsafe or ineffective medical products***." Guidance at 6-7.

# Best Practices

- Updated Training for Sales Force
  - Delineate clear roles and responsibilities throughout the company
  - Require documentation of materials disseminated, just like they would promotional literature
- Balancing Sales and Practice of Medicine
  - Medical device industry more impacted than pharma industry
  - Medical science liaisons should be trained and equipped to engage in specific questions from health care practitioners
- Use of Contract Sales Force
  - FDCA prohibits "causing" the introduction of an adulterated/misbranded device into interstate commerce.
  - Even unrelated parties can be held responsible

# Best Practices

- Consideration of FCA Exposure
  - Government healthcare programs cover off-label uses that are "medically accepted" (i.e., supported by medical literature).
    - FDAMA § 401 and regulations more explicitly spoke to dissemination of information to "pharmacy benefits managers, health insurance issuers, group health plans, and Federal or State governmental agencies."
    - Draft Guidance is not as clear, but references value to health care professionals
  - FCA violation for knowingly causing the presentation of a false claim
- International Implications
  - FDA's jurisdiction is based on the "interstate commerce" element
  - If a manufacturer's conduct causes the introduction of a misbranded device into interstate commerce, then there is an FDCA violation.

# Questions?