DuaneMorris

FDA Regulation of Promotion & Advertising

Part 3: Disseminating Scientific Information

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Overview

- **Tension – FDA, approved labeling and the First Amendment**
- **Manifestations**
  - Scientific information exchange – concern – improper influence by company on content of educational activity
  - Off-Label promotion (to be discussed in Part 6)
  - Our approach – ***disregard "Caronia" for now***
- **Guidance -- Industry-Supported Scientific and Educational Activities *[Hot link]* -- 1997**

1997 Scientific Exchange Guidance

- **To be "safe," must be both independent and non-promotional**
  - if so, not subject to FDA jurisdiction
- **Unapproved uses –** not permissible if program is subject to "substantive influence" by regulated industry
- **Factors influencing "independence" determination**
  - Content influence -- whether and to what extent company can
    - speaker or moderator selection or recommendation, especially if speaker has promoted company's products or were subject of complaints as to past presentations that were biased or misleading in favor of company

» ***… continued …***

1997 Scientific Exchange Guidance …

- **Factors influencing "independence" determination**

  … continued …

  - topic selection, e.g., via targeting points for emphasis
  - scripting done

  – Disclosures to audience –

  - company funding of project
  - relationships between company and speakers (e.g., financial, employee)
  - whether any unapproved uses would be disclosed

  – Program Focus

  - intent to be free of commercial bias (not clear how proved)
  - Title and content really match

1997 Scientific Exchange Guidance …

- **Factors influencing "independence" determination**

  … continued …

  – Program Focus … ***continued***

  - Balanced discussion of all treatment modalities

  – Relationship with provider –

  - e.g., if provider believes continued financial support is dependent on having programs about company products
  - intertwining ownership or control of provider with company

  – Provider involved in sales & marketing – including provider employees

  – Provider's Demonstrated Failure to Meet Standards – of independence, balance, objectivity, or scientific rigor

1997 Scientific Exchange Guidance …

- **Factors influencing "independence" determination**

  … continued …

  – Multiple presentations – of same material – could be factor; FDA recognizes there are benefits to repeated info

  – Audience selection – how done can influence

  - generated by company Sales & Marketing – e.g., to reward big "rx writers" or Key Opinion Leaders (KOLs)

  – Opportunities for discussion – if not present, not good

  – Post-event dissemination of information – except if done via unsolicited request or thru independent provider

  – Ancillary promotional actions –

  - exhibit materials
  - Sales & marketing presentations

1997 Scientific Exchange Guidance …

- **Factors influencing "independence" determination**

  … continued …

  – Complaints – any raised that company tried to influence content

- **Document independence**

  – Contract between company and provider that provides for independence and that provider will be solely responsible for managing program

- **Promotional vs. non-promotional**

  – If supported activity is not about the company's products OR competitive products, is not promotional

Good Reprint Practices

January 2009 – 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 *[Hot Link]***
- **Genesis of guidance**
  - **FDAMA § 401** – had added § 551 of Act (sunsetted in late 2006) – on off-label use dissemination; led to promulgation of 21 CFR Part 99 (also now void) – if complied, would not be used as evidence of intent of off-label use – "safe harbor"
    - limited to HCPs and certain healthcare entities (e.g., PBMs)
    - sunsetting – led to guidance in 2009

Feb. 2014 – New Draft Guidance

- **Distributing Scientific and Medical Publications on Unapproved New Uses – Recommended Practices** ***[Hot Link]***
  - will replace 2009 guidance – still applies only to 3rd party pubs.
  - Key differences:
    - Adds "clinical practice guidelines" (CPGs) to items covered by guidance
    - Clarifies that it also applies to "off-label" promotion of exempt medical devices for uses outside those covered by classification regulation
    - Discusses the different types of documents separately: (1) scientific journal articles; (2) scientific or medical reference texts; and (3) clinical practice guidelines (CPGs)

FDA -- Legal Analysis of Unapproved Use

- **Drug**
  - approved drug marketed for an unapproved use is an unapproved drug for that use – violation of § 505(a) – is a "prohibited act" under § 301(d) of Act
  - unapproved drug that is marketed lacks adequate directions for use in violation of § 502(f) of Act – in turn, it is a prohibited act under § 301 of Act to market a misbranded drug
- **Medical Device –** if promoted for unapproved or uncleared use is also misbranded and adulterated
  - Marketing an adulterated or misbranded device = prohibited act under § 301 of the Act.

The 2014 Draft Guidance

Scientific or Medical Journal Articles

- **Requirements for Publishing Entity**
  - Must have editorial board of experts ('09)
    - independent of the organization that publishes the article
  - Public policy of full disclosure of conflicts of interest for authors, editors, and contributors
- **Article – must:**
  - Be peer reviewed and published per peer review procedure
  - Be an unabridged reprint or copy of article
  - Contain information that:
    - Describes adequate and well-controlled clinical investigations that are considered scientifically sound by experts qualified to evaluate safety or effectiveness of product

Scientific or Medical Journal Articles …

- **Article – must …:**
  - Contain information that is such that … :
    - Devices – articles on following, "also may be consistent with this guidance:"
      - "significant investigations other than adequate and well-controlled studies, such as meta-analyses, if they are testing a specific clinical hypothesis
      - "significant non-clinical research" – such as well-designed bench or animal studies
  - Send with approved labeling for each product discussed in article
  - Send with a "comprehensive bibliography" of other articles about the off-label use (pro or con) – unless the bibliography is in article

Scientific or Medical Journal Articles …

- **Article – must …:**
  - Send with a "representative publication" (if existing) that reaches contrary or different conclusions on unapproved use, especially those calling into question the article you are sending
  - Send separately from any promotional material
    - If a sales rep get a question on the article, rep must direct questioner to a medical/scientific department that is independent of sales/marketing
    - Can't disseminate in the exhibit hall of a conference or during promotion speakers' programs
- **Article – must not:**
  - Be false or misleading
  - Suggest a use that is dangerous to health

Scientific or Medical Journal Articles …

- **Article – must not:**
  - Be funded, wholly or partially, be the maker of the product
  - Be "marked, highlighted, summarized, or characterized" by product maker to "emphasize or promote" the off-label use
  - Be primarily distributed by product maker; *rather*, must be generally available publicly where periodicals are sold
  - Be written, edited, excerpted or published at request of product maker
  - Be edited or "significantly influenced"**** by product maker or any individual having a "financial relationship" to product maker
    - **** see discussion on influence on ISSEA (slides 3 to 7, *infra*)

Scientific or Medical Journal Articles …

- **Article – must not:**
  - Be attached to any product info other than approved labeling or cleared indications for use statement
- **Reprint should be accompanied by a "prominently displayed and permanently affix statement" that:**
  1. Lists the drugs or devices in the reprint in which product maker has an interest
  2. That some (or all) of the uses in the article have not been blessed by FDA "as applicable to the described drug(s) or device(s)"
     - I interpret that you have to say which uses are not blessed

Scientific or Medical Journal Articles …

- **Reprint should be accompanied by a "prominently displayed and permanently affix statement" that … :**
  3. Lists any author "known to the manufacturer" as having a financial interest in the mfr. or the product of the mfr. or receiving compensation from the mfr.; must state:
     - Nature and amount of financial interest
     - Affiliation of author
  4. States any person known to the mfr. to have funded the study
  5. All significant risks or safety concerns associated with the unapproved use that are known to mfr., but not discussed in article
     - ***Note***: no direct mandate to do a literature search; however, one should be done for liability reasons

Scientific or Medical Journal Articles …

- **Unacceptable Reprints**
  - 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

Scientific or Medical Reference Texts

- **Handled separately under guidance because texts are much longer than articles, but still may discuss off-label uses**
- **If disseminated in its entirety, must:**
  1. Be based on a systematic review of the existing evidence
  2. Be published by an independent publisher that is:
     - not "substantially dependent on financial support" from drug or device mfrs.; and
     - Who publishes scientific or medical educational content for health care professional and students
  3. Be the most current version

Scientific or Medical Reference Texts …

- **If disseminated in its entirety, must …:**
  4. Be authored, edited or contributed by experts with "demonstrated expertise" on subject
  5. Be peer-reviewed per published peer-review procedures of the publisher
  6. Sold through "usual and customary" independent channels directed at HCP's and students
  7. Be distributed separately from promotional materials
     - ➢ If a sales rep get a question on the article, rep must direct questioner to a medical/scientific department that is independent of sales/marketing
     - ➢ Can't disseminate in the exhibit hall of a conference or during promotion speakers' programs

Scientific or Medical Reference Texts …

- **If disseminated in its entirety, must …:**
  8. Contain prominently displayed and permanently affixed statement that:
     - Some of the uses may be off-label
     - Some of the authors might have a financial interest in the mfr. or product being written about, unless mfr. verifies that none of the authors has such a financial interest
  9. If a text contains a chapter with a "primary substantive discussion" to mfr.'s product, have to send with the product labeling for each discussed product.

Scientific or Medical Reference Texts …

- **If disseminate a single chapter, must:**
  1. Meet above criteria for entire text, subject to modifications
  2. Be unaltered/unabridged and directly extracted from the text in which chapter appears
  3. If "necessary to provide context," must disseminate with other chapters from the same text
  4. Contain prominent and permanently affixed statement identifying the mfr. and disclosing:
     - Drug or device in which mfr. has an interest
     - That some or all of the uses are off-label
     - Disclosure of financial interests in the mfr. or product of any author, including author's affiliation and nature of fin. interest

Scientific or Medical Reference Texts …

- **If disseminate a single chapter, must …:**
  - Disclose "all significant risks or safety concerns" associated with the unapproved uses that are known to mfr. but not discussed in the chapter
  - Disseminate with the approved labeling for each product in the chapter
- **Can't be:**
  1. False or misleading
  2. Suggest a use that makes product dangerous to health

Scientific or Medical Reference Texts …

- **Other restrictions:**
  - Must be generally available in publishing channels; can't be primarily distributed by the mfr.
  - Can't be edited or significantly influenced by mfr. or by individuals have a financial relationship with the mfr.
  - Can't be marked, highlighted, summarized, etc. as to the unapproved use, verbally (e.g., by sales rep) or in writing
  - Can't be written or published specifically at the request of the mfr.
  - Can't be abridged or excerpted (except for sending a single chapter consistent with the guidance)
  - Can't be attached to product information, except for approved labeling

Clinical Practice Guidelines (CPGs)

- **CPG Defined:**
  - Statements that include recommendations intended to help clinicians make decisions for individual patient care, including in circumstances where there are few or no approved drugs or devices indicated for the patient's condition or the approved therapies have not "proven successful" for the patient
  - IOM – has standards for CPG "trustworthiness" that the Guidance incorporates

Clinical Practice Guidelines (CPGs) …

- **IOM – standards for CPG "trustworthiness"**
  1. Based on systematic review of "existing evidence"
  2. Developed by a knowledgeable, multidisciplinary panel of experts and reps from key affected groups
  3. Consider important patient subgroups and preferences
  4. Be done via an explicit and transparent process, including funding, that minimizes bias, conflicts, and distortions
  5. Clearly:
     - Explain logical relationships between alternative care options and health outcomes
     - Provide articulated recommendations in a standardized form
     - Rate both quality of evidence and strength of recommendations
  6. Be reconsidered and revised if new evidence warrants

Clinical Practice Guidelines (CPGs) …

- **If CPG is trustworthy, to distribute, a mfr. *should***
  1. Ensure most recent CPG is distributed
  2. Do not send with promotional material (same basic restrictions, including referral to medical/scientific affairs by sales reps, as with articles)
  3. Contain the prominently affixed statement as to off-label contents (same as with articles)
  4. If "primary substantive discussion" occurs of the mfr.'s product, must send with approved labeling

Clinical Practice Guidelines (CPGs) …

- **If send only individual sections of a CPG, a mfr. *should:***
  1. Contain a permanent statement unique to sections, as opposed to an entire CPG
  2. Be unaltered/unabridged and directly extracted from the text in which chapter appears
  3. If "necessary to provide context," must disseminate with other chapters from the same text

Clinical Practice Guidelines (CPGs) …

- **If send only individual sections of a CPG, a mfr. *should:***

4. Contain prominent and permanently affixed statement – on front of each section -- identifying the mfr. and disclosing:
   - Drug or device in which mfr. has an interest
   - That some or all of the uses are off-label
   - Disclosure of financial interests in the mfr. or product of any author, including author's affiliation and nature of fin. Interest
   - Disclose "all significant risks or safety concerns" associated with the unapproved uses that are known to mfr. but not discussed in the chapter
5. Disseminate with the approved labeling for each product in the chapter

Clinical Practice Guidelines (CPGs) …

- **Must not be:**
  1. False or misleading
  2. Suggest a use that makes product dangerous to health
- **Should not be:**
  1. Primarily distributed by the mfr.; must be generally available in publishing channels;
  2. Edited or significantly influenced by mfr. or by individuals have a financial relationship with the mfr.
  3. Marked, highlighted, summarized, etc. as to the unapproved use, verbally (e.g., by sales rep) or in writing
  4. Written or published specifically at the request of the mfr.
  5. Abridged or excerpted (except for sending a single chapter consistent with the guidance)
  6. Attached to product information, except for approved labeling

How it Worked under the 2009 Guidance

(for you history buffs)

Permissible Reprints -- Types

- **Published by an organization that has an editorial board that:**
  - uses experts with demonstrated expertise in the subject of the article under review by the organization and who are independent of the organization to review and objectively select, reject, or provide comments about proposed articles; and
  - that has a publicly stated policy, to which the organization adheres, of full disclosure of any conflict of interest or biases for all authors, contributors, or editors associated with the journal or organization;
- **Must be peer-reviewed --** and published in accordance with the peer-review procedures of the organization; and
- **Not be in the form of a special supplement or publication that has been funded** in whole or in part by one or more of the manufacturers of the product that is the subject of the article.

Permissible Reprints -- Types

- **Excluded characteristics**
  - Can't be primarily distributed by a drug or device manufacturer,
    - Should be generally available in bookstores or other independent distribution channels (e.g. subscription, Internet) where medical textbooks or periodicals are sold;
  - Can't be written, edited, excerpted, or published specifically for, or at the request of, a drug or device manufacturer; or
  - Can't be edited or significantly influenced by a drug or device manufacturer or any individuals having a financial relationship with the manufacturer.

Content

- **<u>Required</u> – to address 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 or device.
  - These can include historically controlled studies, pharmacokinetic (PK) and pharmacodynamic (PD) studies, and meta-analyses if they are testing a specific clinical hypothesis
- **<u>Excluded</u> –**
  - Be false or misleading
  - Pose a significant risk to the public health, if relied upon

Distribution Manner

- **Unabridged reprint, copy of an article, or reference publication –** note– does not have to be solicited
- **Not be marked, highlighted, summarized, or characterized by the manufacturer in any way**
  - except for disclosures required by the guidance
- **Be sent with the approved labeling for product**
- **Be sent with a comprehensive bibliography --**
  - discussing adequate and well-controlled clinical studies published in medical journals or medical or scientific texts about the use of the drug or medical device covered by the information disseminated (unless the information already includes such a bibliography)

Distribution Manner …

- **Sent with a representative publication, when such information exists, that reaches contrary or different conclusions regarding the unapproved use;**
  - especially where the conclusions of articles or texts to be disseminated have been specifically called into question by another published article(s) or text(s)
- **Must not include any promotional information**
  - can be delivered by sales rep, but must be free of any promotional info and can't be discussed by rep
  - can be handed out at a medical or scientific conference, must not be in exhibit halls or during a promotional presentation

Disclaimers Required

- **Reprint must be accompanied by a "prominently displayed and permanently affixed statement" disclosing:**
  - that the uses described in the information have not been approved or cleared by FDA, as applicable to the described drug or medical device;
  - the manufacturer's interest in the drug or medical device that is the subject of the journal reprint or reference text;

Disclaimers Required …

- **Reprint must be accompanied by a "prominently displayed and permanently affixed statement" …**
  - any author known to the company as having a financial interest in the product or company or who is receiving compensation from the company, along with the affiliation of the author, to the extent known by the company, and the nature and amount of any such financial interest of the author or compensation received by the author from the company;
  - any person known to the company who has provided funding for the study; and
  - all significant risks or safety concerns known to the manufacturer concerning the unapproved use that are not discussed in the reprint.

Distributing Scientific Publications on Risk Information

June 2014 Draft Guidance

Off-Label Promotion of ***Safety/Risk*** Info

- **June 2014 – Draft Guidance – "Distributing Scientific and Medical Publications on Risk Information for Approved Prescription Drugs and Biological Products – Recommended Practices"**

  [Hot Link]

  – Products subject to the D.G.:
    - Rx drugs and biologics
    - Rx and OTC animal drugs and medicated feed

  – D.G. only applies to risk info that makes a change that is ***less serious*** than that which is in approved labeling – "rebuts, mitigates … or otherwise refines risk information in the approved labeling."

Off-Label Promotion of ***Safety/Risk*** Info …

- **Distribution – limited to these recipients**
  - "healthcare professionals" -- those providing care to either humans or animals
  - "healthcare entities" – hospitals, professional medical organizations, group health plans, federal or state agencies "involved in the provision of health care or health insurance."
- **Data source**
  - Study or analysis should meet accepted design and methodologies for the type of analysis being done
  - To rebut a prior finding, study must be "at least as persuasive as the data sources" that formed basis for the statement in approved labeling being rebutted

Off-Label Promotion of ***Safety/Risk*** Info …

- **Data sources …**
  - Conclusions must give appropriate weight and consideration of all relevant info in the safety database
  - Must be published in an independent, peer-reviewed journal
- **Distribution Requirements – with a cover sheet that:**
  - Includes study design, methodologies and limitations
  - Says info is not consistent with specifically identified parts of the approved labeling
  - Say that FDA has not reviewed the data
  - Disclose any financial interests or affiliations between study author(s) and firm distributing info
  - Can't include promo materials

Responding To Unsolicited Requests for Off-Label Information

December 2011 – Draft Guidance

- **Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices** ***[Hot Link]***
  - Applies to
    - approved drugs and biologics (human and animal)
    - approved and cleared devices
    - Off-label also includes deviating from intended uses in device classifications for devices that are 510(k) exempt
  - Not applicable to investigational products
  - Dissemination of info on off-label uses – can be seen as "evidence of a new intended use" – without approval/clearance – violates law

December 2011 – Draft Guidance …

- **Applies to unsolicited requests made directly or indirectly** – e.g., in public internet sites
- **If respond consistent with guidance**, FDA will not use the response as "evidence of the firm's intent that the product be used for an unapproved or uncleared use."
- **Responses** – not expected to comply with normal disclosure of information rules for advertising or labeling
- **Solicited requests** – not subject to draft guidance, but can be evidence of intent by firm of an off-label use for its product – implied message of guidance – ***DON'T***

December 2011 – Draft Guidance …

- **FDA – Acceptable to reply to unsolicited requests for off-label info on FDA-regulated medical products:**
  - "by providing truthful, balanced, non-misleading, and non-promotional scientific or medical information that is responsive to the specific request, even if responding to the request requires a firm to provide information about unapproved or uncleared indications or conditions of use."
- **Response – whether to a private or public solicitation –** should be in a private, one-on-one communication, to the person who requested.

Private Requests – Responding

- **Two key aspects of response:**
  - Should be in a private, one-on-one communication, to the person who requested.
  - Response should be "tailored to answer only the specific question(s) asked."
    - if get a broad question, should try to narrow the focus
    - however, if risk information exists that relates to the question, but is not directly on point to the question, should include
      - ***Example:*** question about use in pregnancy and diabetes; risk info exists on fetal harm when used in arthritis – disclose fetal harm issue even though off-label use asked about was re diabetes

Private Requests – Responding …

- **Response must be "truthful, non-misleading, accurate and balanced"**
  - must include info that would cast doubt or are non-supportive of off-label info
  - should include complete copies of articles referenced
  - to "extent possible," should rely on peer-reviewed journals, medical texts, and independent sources of info.
    - but, can use "data on file"
    - journals – should be from those will full disclosure info on authors as to conflicts and biases
- **Must be "scientific" in tone**

Private Requests – Responding …

- **Should be generated by medical or scientific personnel –** independent of sales or marketing
- **Responders** – should be trained on how to reply (consistent with the guidance)
- **Info to send with response:**
  - FDA approved labeling, including any patient labeling
  - "Prominent statements"
    - FDA has not approved/cleared the off-label info enclosed
    - As to what uses are FDA approved/cleared
    - All important safety info re product, including boxed warning
    - complete list of references

Private Requests – Responding …

- **Recordkeeping**
  - Nature of request for information
  - Name, address and affiliation of requestor
  - What was provided to the requestor
  - Any follow-up requests or inquiries from requestor

Public Requests -- Responding

- **Only respond if it is specifically about your product (and not just your competitor's) –** even if you have info on your product that would respond to the request
- **Public response – limited –** just provide contact information – scientific or medical -- for more info
  - but, FDA wants you to say in your public response that the request relates to an off-label use
  - contact info -- be specific (e.g., e-mail address; phone; fax)
  - assumption – until you then get a private inquiry, nothing more you can do
  - "public responder" – must make clear they are with the company

Public Requests -- Responding

- **Public response … continued …**
  - must be non-promotional
  - must include info on how to access **just** the approved labeling and not any other website that is promotional
    - the URL for labeling must be non-promotional (e.g., can't be www.bestforgout.com)

End of Part 3 – Disseminating Scientific Information