EPSTEIN BECKER GREEN

Digital Device Labeling and Promotion

presented by Bradley Merrill Thompson

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Topics

I feel like Zsa Zsa Gabor's fifth husband. I know what I'm supposed to do but I don't know if I can make it interesting.

- Al Gore

Part One - Regulatory Requirements

Part Two - Claim Substantiation

Part Three - Off-Label Promotion

Part Four - Marketing in a Regulated Environment

Agenda

Part One:

Regulatory Framework for Product Promotion

Topics

1. Definitions
2. Fundamental prohibition
3. Special labeling rules
4. Off-label promotion

> Politics gives guys so much power that they tend to behave badly around women. And I hope I never get into that.
>
> -Bill Clinton

Definitions

“Label" is:

A display of written, printed, or graphic matter upon the immediate container of any article....

“Labeling" is:

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.

Definitions

“**Accompanying**":

- Is interpreted liberally to mean more than physical association with the product
- Extends to posters, tags, pamphlets, circulars, booklets, brochures, instruction books, direction sheets, etc., depending on how they are used
- Includes labeling that is brought together with the device after shipment or delivery for shipment in interstate commerce.
- Can also include website content and other information a manufacturer posts online

But what of a tweet or a post on a discussion board?

FDA Regulation of Advertising

Advertising

- Not defined in the FFDCA
- FDA likes to treat advertising as labeling
  - According to an appellate court decision: "Most, if not all advertising, is labeling.... Congress did not, and we cannot, exclude from the definition printed matter which constitutes advertising."
- Advertising includes:
  - Journal and magazine ads
  - Television or radio commercials
  - Direct mail or email communications
  - Certain online promotion
- FDA regulates labeling and restricted device advertising

The Ten Commandments contain 297 words.
The Bill of Rights 463 words.
The Gettysburg Address 266 words.
A recent federal directive to regulate the price of cabbage contains 26,911 words.

Fundamental Prohibition

The term misbranded means:

- "False or misleading in any particular."
  - False generally is understood to mean a statement that in any material respect is untrue.
  - Misleading is less clear (to whom and how much?)
- Twin goals of —
  - Safety and effectiveness
  - Preventing economic fraud

False Labeling

Examples include:

- Incorrect, inadequate or incomplete identification
- Unsubstantiated claims of therapeutic value
- Substitution of parts or material
- Inaccuracies concerning condition, state, treatment, size, shape or style

Misleading Labeling

Examples include:

- Ambiguity, half-truths, and trade puffery
- Expressions of opinion or subjective statements
- Failure to reveal material facts, consequences that may result from use, or the existence of difference of opinion

Risk Information and Intended Uses

May 2009 proposed guidance explains claims must be truthful, not misleading, fairly balanced and substantiated

- Manner of presentation of risk and benefit determines net impression
- FDA considers quantity, materiality and comprehensiveness of risk and benefit information
- The format of risk and benefit information is important in determining net impression

Other Misleading Labeling

Examples:

- Deceptive pictorial matter
- Misleading testimonials
- Misleading list of parts or components
- Use of brand or trade names instead of "established names"

> Often the surest way to convey misinformation is to tell the strict truth.
>
> -Mark Twain

What Else Is Misbranded?

FDA specifically requires certain information, prominently displayed (unless exempt):

- Established name of the product
- Name and place of business of the manufacturer, packer, or distributor
- Net quantity of contents
- Adequate directions for use and adequate warnings

Exemptions from Adequate Directions for Use

- Prescription devices
- Commonly-known directions
- IVDs
- Products intended for further processing
- Teaching, law enforcement and research

Investigational Device Labeling Rules

Promotion and commercialization of devices subject to an IDE is prohibited

- Promotion of clinical trial results (needs to be bona fide scientific exchange)
  - Tone
  - Context
- Disclosure of commercial price
- Taking or being prepared to take orders
- Prolonging the investigation

FTC Regulation of Advertising

- FTC has jurisdiction over advertising for a non-restricted device
- FTC applies three requirements
  - Adequate substantiation
  - No deception, from the standpoint of the reasonable consumer
  - Fairness
- Agency influenced by lawyers who focus on consumers and how they are affected

FTC Rules on Endorsements and Testimonials

- Guidance Revised 2023
  - 16 C.F.R. Part 255
- **Endorsements don’t relieve any rules, instead they just add requirements**
  - Endorsements must reflect the honest opinions, findings, beliefs, or experience of the endorser
  - An endorsement may not convey any express or implied representation that would be deceptive if made directly by the advertiser
  - Advertisers are subject to liability for false or unsubstantiated statements in endorsements
  - Material connections between the endorser and the seller must be fully disclosed
- You quote it, you own it
- Has significant implications for social media

Lanham Act

- Action against a competitor in federal court
- Liability arises from deceptive statements about either the competitor's or the company's own product alleged to harm the other party, including:
  - False or misleading claims
  - Unsubstantiated comparative claims
  - Overstatements of efficacy
  - Minimization of risks
- Damages & injunctive relief are available

State Regulation of Advertising

- State Food Drug & Cosmetic Acts
- State consumer protection laws
  - Enforcement by state attorneys general
  - Consumer class actions

I have always wanted to be somebody. I guess I should have been more specific.

-Lily Tomlin

Interactions with Physicians

- Applicable law
  - Federal Anti-kickback statute
  - Fraud and Abuse provisions of the Social Security Act (Medicare/Medicaid)
  - Federal False Claims Act
  - State Anti-kickback statutes
  - State False Claims Acts
  - State statutes requiring disclosure of gifts to prescribers
- AdvaMed Code

Types of Interactions

Government enforcement risks arise in the context of:

- Business courtesies
  - Ensure sales personnel follow applicable guidance with respect to gifts, meals and entertainment
- Consulting arrangements
  - Consulting arrangements must be for necessary services pursuant to written agreements in compliance with regulatory requirements
- Research grants
  - Grants should be administered outside marketing function, based on objective criteria
- Educational activities & meetings
  - Sponsored meetings must take place in locations conducive to educational activities, without providing entertainment and with only modest meals and accommodations

Agenda

Part Two:

Claim Substantiation

Topics

1. Generally
2. Comparative claims

> The pure and simple truth is rarely pure and never simple.
>
> -Oscar Wilde

FDA Claim Substantiation

- Refers to the evidence needed to support a claim regarding some feature or performance of the device
  - Must support both express and implied claims
  - In labeling, revolves around the FDCA “false and misleading” language
  - In advertising, revolves around the FTC standard requiring a reasonable basis in objective evidence before the claim is made
- Unlike with drugs, there is no explicit FDA guidance on device claim substantiation

FTC Factors for Adequate Substantiation at Time of First Use

- Type of product
- Type of claim
- Benefits of a truthful claim
- Cost/feasibility of developing substantiation for the claim
- Consequences of a false claim
- Amount of substantiation that experts in the field believe is reasonable

Comparative Claims

- These compare the device to another device
- FDA considers them inherently misleading
  - Requires that such claims be supported by sound scientific data, usually a rigorous study that directly compares the devices
- FTC does not have that same predisposition, instead favoring useful comparisons
  - But likewise requires rigorous scientific evidence, again a study or studies comparing the devices

Agenda

Part Three:

Off-Label Promotion

1. Off-Label Use Rules
   i. Basic Intended Use Framework
   ii. Evolution of the Legal Landscape
2. First Amendment Issues

Winter related injuries occur more often in the winter.

-newswoman for WHIZ-TV, Zanesville Ohio

Tension: Freedom to Practice Medicine

21 U.S. Code § 396

"Nothing in this chapter shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship… this section shall not change any existing prohibition on the promotion of unapproved uses of legally marketed devices."

Basic Rule: Amended Regulation

21 CFR 801.4 revised August, 2021

Sec. 801.4 Meaning of intended uses.

The words intended uses or words of similar import in ~~§§~~ §§ 801.5, 801.119, ~~and~~ 801.122, and 1100.5 of this chapter refer to the objective intent of the persons legally responsible for the labeling of ~~devices~~ an article (or their representatives). The intent ~~is determined~~ may be shown by such persons' expressions ~~or may be shown~~, the design or composition of the article, or by the circumstances surrounding the distribution of the article. This objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives. ~~It~~ Objective intent may be shown, for example, by ~~the~~ circumstances ~~that~~ in which the article is, with the knowledge of such persons or their representatives, offered ~~and~~or used for a purpose for which it is neither labeled nor advertised; provided, however, that a firm would not be regarded as intending an unapproved new use for ~~an approved or cleared device~~a device approved, cleared, granter marketing authorization, or exempted from premarket notification -based solely on that firm's knowledge that such device was being prescribed or used by health care providers for such use.~~–~~The intended uses of an article may change after it has been introduced into Interstate commerce by its manufacturer. If, for example, a Packer, distributor, or seller intends and article for different uses than those intended by the person from whom he or she received the ~~devices~~article, such Packer, distributor, or seller is required to supply adequate labeling and accordance with the new uses. ~~But if a manufacturer knows, or has knowledge of facts that would give him notice that a device introduced into Interstate commerce by him is to be used for conditions, purposes, or uses other than the ones for which he offers it, he is required to provide adequate labeling for such a device which accords with such other uses to which the article is to be put.~~

Judging Intended Use

It's Facts and Circumstances: Look at the Evidence

Words

a. External (e.g. labeling, sales lit., advertising, sales pitches)
b. Internal (e.g. business planning, sales force memos, training programs)

Actions

a. Design features (i.e. uniquely medical features)
b. Distribution (e.g. medical sales and distribution channels)
c. Where do your sales people visit?

Circumstances

a. How legitimate are labeled uses?
b. Sales volume related to off label use

Summary of Off-Label Use Rules:

Basic Prohibition

- If an intended use for a distributed device is not a lawful one:
  - Lack of approval for the intended use makes the device “adulterated”
  - The lack of adequate labeling makes the device “misbranded”
- Determining intended use, and therefore a violation, is a facts and circumstance test
  - Multifactor test: words, deeds and circumstances
  - FDA willing to exclude certain evidence from consideration
  - Weigh the evidence to determine intended use
  - Is the intended use an unlawful one?

Evolution of the Legal Landscape

Over the years:

- FDA's authority to regulate off-label promotion has been limited by the courts
  - Washington Legal Foundation (1999)
  - Western States Medical Center (2002)
  - Caronia (2012)
  - Amarin Corp. (2015)
  - Vascular Solutions (2016)

- FDA cannot infringe on the right of medical device companies to share truthful information: on- or off-label.
- But Supreme Court has held that "the First Amendment … does not prohibit the evidentiary use of speech to establish the elements of a crime or to prove motive or intent." FDA Memorandum in public docket, January 2017

SEC Disclosure Requirements

- SEC's requirement that companies disclose material information to the investment community, including both positive and negative results of clinical trials, is sometimes inconsistent with FDA's limitations on disclosure
  - Clash of pro-speech policy with FDA's speech restrictions
- SEC has brought enforcement actions against companies for failure to disclose important information about products in clinical trials

Agenda

Part Four:

Sharing Information in Safe Harbors

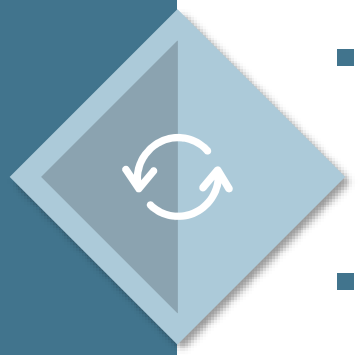
1. Good Reprint Practices
2. Unsolicited Requests
3. Investor Communications
4. Trade Shows
5. Scientific Meetings
6. Health Care Economic Information

> The voters have spoken—
> the bastards.
>
> -Richard M. Nixon

Development Phases

Phase	Regulatory Category	Requirements Related to Promotion
1	Early Development	As a legal technicality, none on promotion until introduced into interstate commerce. See CPG 300.600. Remember design control requirements that will apply to labeling. But customers and FDA will remember what is said.
2	Investigational (Human use)	IDE regulation places explicit restrictions. For example, no promotion is allowed beyond what is necessary for its use in investigations (e.g. recruiting subjects). Here, no clinical performance claims are permitted.
3	510(k) pending	According to FDA CPG section 300.600: "Although a firm may advertise or display a device that is the subject of a pending 510(k)--in the hope that FDA will conclude that the device is substantially equivalent to a pre-amendments device--a firm may not take orders, or be prepared to take orders, that might result in contracts of sale for the device unless limited to research or investigational use."
4	Cleared or approved	A whole slew of restrictions apply, including limits on off-label promotion, truth in labeling, adequate directions for use, and a number of affirmative requirements related to name, quantity, etc...
5	Cleared and investigational	A blend of both phase 2 and 4.

FDA Guidance: Good Reprint Practices



- An opportunity for medical device companies to hand out scientific reprints without causing the device to be misbranded, or otherwise constituting off label promotion (2009)
- Lots of strings attached
  - Publishing Organizations must be legit
  - Channels of Distribution must be legit.
  - Influence of the Manufacturer in the content of the article must be avoided.
- Update proposed “Distributing Scientific and Medical Publications on Unapproved New Uses—Recommended Practices” February 2014
  - Different rules for different types

Good Reprint Practices

Quality of Disseminated Information

Must not pose a significant risk to the public health.

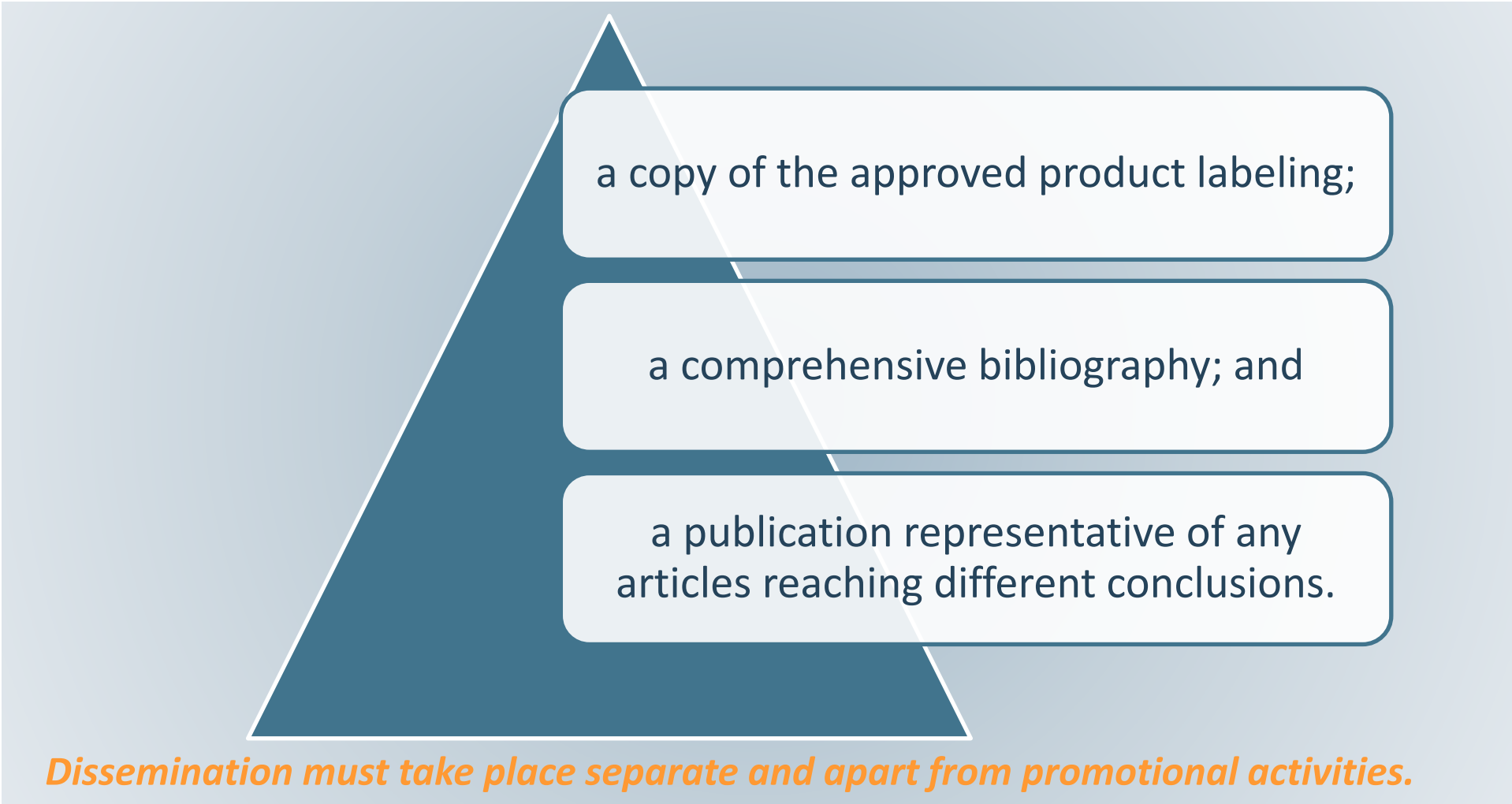
Must address sound evidence.

Must be truthful and not misleading. For example, avoid information that is inconsistent with the weight of credible evidence

Must be disseminated in its original state.

Good Reprint Practices

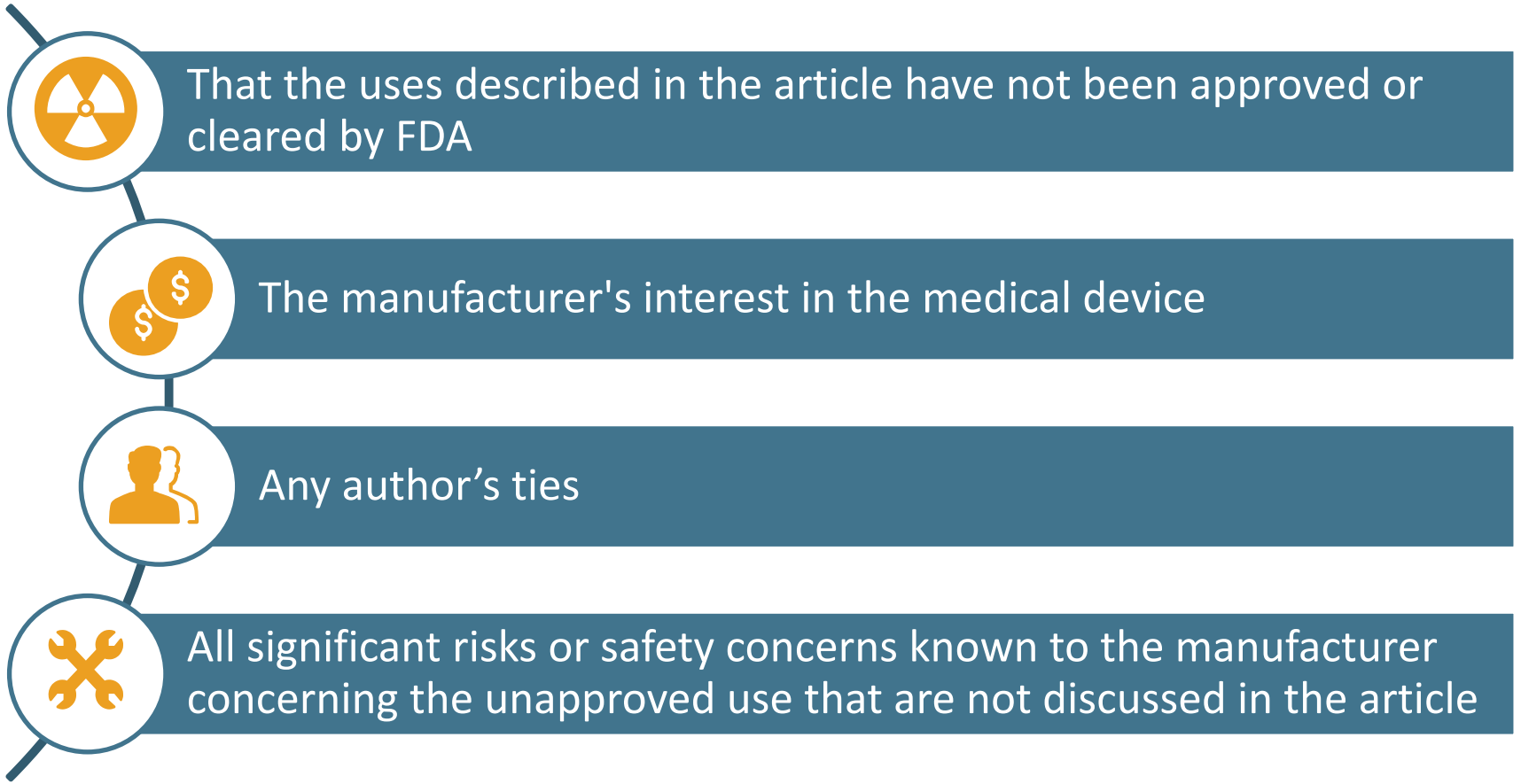
Accompanying Information



Dissemination must take place separate and apart from promotional activities.

Good Reprint Practices

Disclaimers and Disclosures



Unsolicited Requests

- Proposed Guidance (December 2011)
- Recognizes the value of responding to such requests, and the important information manufacturers possess
- Divides the universe of requests into
  - private and
  - public requests

What is Unsolicited?

Unsolicited requests are those initiated by persons or entities that are completely independent of the relevant firm.

Example 8:

A firm asks or otherwise encourages users to post videos about their own uses of its product on third-party video-sharing sites (e.g., YouTube), which may result in video postings about an off-label use of its product. If the firm's initial request for posting of videos results in any questions about off-label uses, or if any off-label video posting made in response to the firm's encouragement of video postings results in questions about the product's off-label use, these questions would be considered solicited requests.

Private Requests

Quality content

1. Private, one-on-one communication.
2. Tailored to answer only the specific question asked.
3. Truthful, non-misleading, accurate, and balanced
4. Scientific in nature — tone
5. Generated by medical or scientific personnel independent from sales or marketing departments

Private Requests (Cont.)

6. Accompanied by the following:
   i. A copy of the FDA-required labeling
   ii. A prominent statement that FDA has not approved the product for the use addressed in the materials provided
   iii. A prominent statement disclosing the indication(s) for which FDA has approved or cleared the product
   iv. A prominent statement providing all important safety information
   v. A complete list of references for all of the information disseminated in the response

Private Requests (Cont.)

7. A firm should maintain the following records:
   i. The nature of the request for information, including the name, address, and affiliation of the requestor
   ii. Records regarding the information provided to the requestor
   iii. Any follow-up inquiries or questions from the requestor

Public Requests

- Applies to real or virtual forums
- Policy—FDA worried about:
  - Others seeing off label uses indefinitely
  - Information becoming out of date
- Guidance
  - Respond only to questions about your product
  - Don’t answer, but instead direct to medical affairs
  - Disclose your involvement
  - Don’t promote

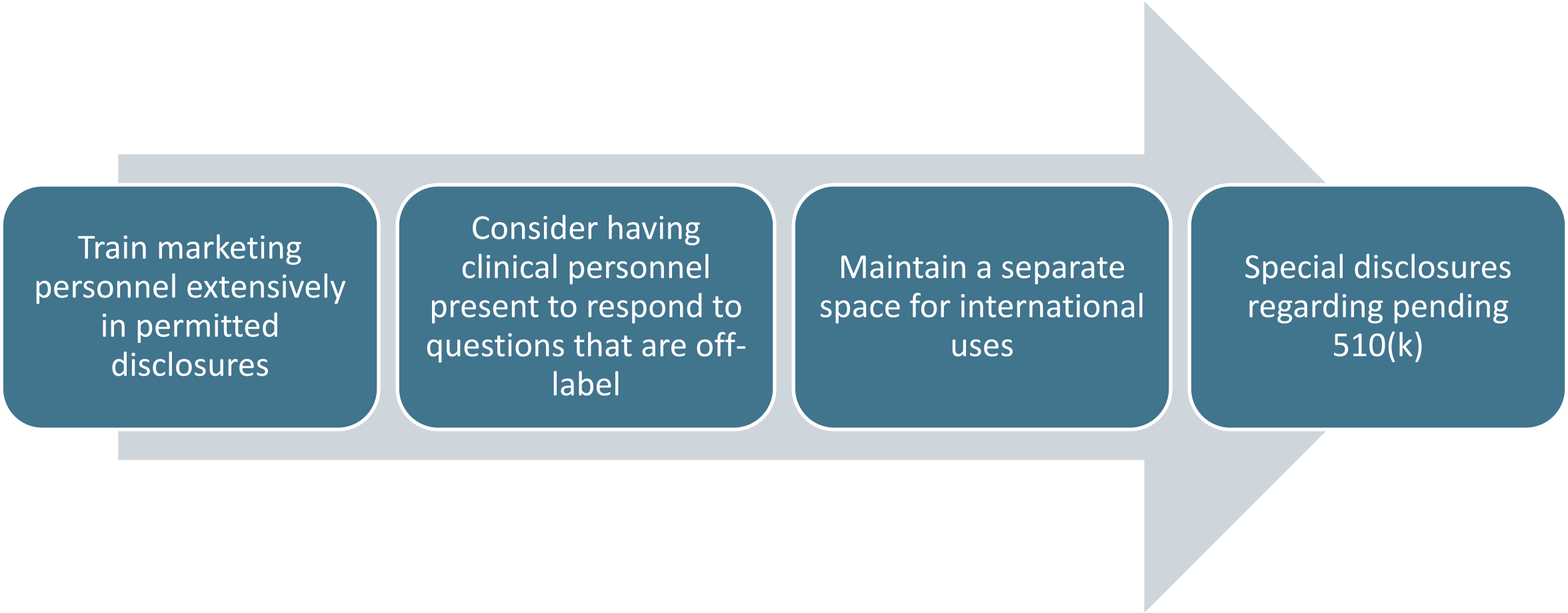
Medical Affairs

- Long recognized by FDA as a position that has additional freedom to engage in bona fide medical and scientific exchange
- Should not report to marketing or sales —must remain independent
- Must maintain its credibility
- Must have medical/scientific credentials,
  - Education
  - Experience

Investor Communications Re: Investigational Uses

- Labeling regulations apply, unless disclosure can be classified as purely business exchange
- Pre-approval off-label information, including study announcements, will be tolerated by FDA if segregated in the investor or news section of a website and/or distributed to the press concurrently with a newsworthy event.
- Must avoid--
  - Promotional tone
  - Claims re safety or effectiveness
  - Redistribution
  - Undue prolonging

Best Practices: Trade Shows



Scientific Meetings – Two Types

Controlled

Speakers under the control of the sponsor (e.g., employees, consultants)

- Investigator meetings
- Speaker training
- Trade show booths

Supported

Speakers are not under the sponsor's control but sponsor provides support for the program

- Sponsored CME

Meetings – Controlled Communications

- Regulated as promotional material
- Remarks should:
  - Be consistent with intended use
  - Conform to rules applicable to unsolicited requests

Meetings – Supported Communications

- Unregulated scientific exchange, unless sponsor is in a position to influence the presentation of information about its products
- In determining independence, FDA will consider:
  - Sponsor's control over content and speakers
  - Meaningful disclosure of sponsor support, relationships with speakers, regulatory status of any unapproved uses discussed
  - Focus of the program (e.g., on a single product or single company's products when alternatives are available)
  - Relationship between provider and sponsor
  - Etc. in 1997 Guidance

Health Care Economic Information

- Guidance: “Drug and Device Manufacturer Communications With Payors, Formulary Committees, and Similar Entities—Questions and Answers” June 2018
- Applies FDCA section 502(a) to devices
- Permits broader use content in the context of economic decision-making
  - Communicated to sophisticated nonprescribers involved in the business of medicine
- Applies the FTC standard of “competent and reliable scientific evidence” for substantiation of claims

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Concluding Thought

Be Proactive

Big Picture Strategy

Have a legitimate reason for doing what you do

- Narrow and tailored
- Focus on legitimate purpose

Good Promotional Practices

- Many leading companies are developing their own GPPs and GRPs
- Essentially a risk management tool — sets the company's preferred path forward in a gray area
- Looked favorably upon by regulators if done well.
- Become the basis for training and auditing

Comments or Questions?

Arguing with a lawyer is like mud wrestling with a pig: after a while you realize that the pig actually enjoys it.