KING & SPALDING

Dissemination of Non-Promotional Information

October 12, 2021

FDLI

INTRODUCTION TO ADVERTISING AND PROMOTION FOR MEDICAL PRODUCTS

Food and Drug Law Institute

PRESENTED BY:

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Agenda

Key Concepts

First Amendment Jurisprudence

FDA Guidance

Role of Medical Science Liaisons

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Key Concepts

Intended Use

Fundamental to FDA's regulation of drugs and medical devices

Kefauver-Harris Amendments of 1962

- Required a showing of safety and efficacy for each new intended use prior to marketing

21 C.F.R. §§ 201.128 (drugs) and 801.4 (devices)

- The "intended use" of a product is the primary basis for determining whether and how a product is regulated by FDA
  - Objective intent of the persons legally responsible for the labeling of drugs
  - Determined by such persons' expressions or the circumstances surrounding the distribution of the product
  - For example: labeling claims, advertising matter, or oral or written statements

Intended Use

Fundamental to FDA's regulation of drugs and medical devices

21 C.F.R. §§ 201.128 (drugs) and 801.4 (devices)

- Recent amendment efforts
  - 2015 Proposed Rule (80 Fed. Reg. 57756 (Sept. 25, 2015))
  - 2017 Final Rule (82 Fed. Reg. 2193 (Jan. 9. 2017))
    - As of January 2018, effective date was delayed indefinitely (83 Fed. Reg. 2092 (Jan. 16, 2018))
  - 2020 Proposed Rule (85 Fed. Reg. 59,718 (Sep. 23, 2020))
  - 2021 Final Rule (86 Fed. Reg. 41383 (Aug. 2, 2021))

Intended Use

2021 Final Rule - Revisions to 21 C.F.R. § 201.128

The words *intended uses* or words of similar import in §§ 201.5, 201.115, 201.117, 201.119, 201.120, 201.122, and 1100.5 of this chapter refer to the objective intent of the persons legally responsible for the labeling of an article (or their representatives) ~~of drugs~~. The intent may be shown ~~is determined~~ by such persons' expressions, the design or composition of the article, or ~~may be shown~~ 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 or ~~and~~ 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 drug based solely on that firm's knowledge that such drug 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 an article for different uses than those intended by the person from whom he or she received the article ~~drug~~, such packer, distributor, or seller is required to supply adequate labeling in accordance with the new intended uses. ~~But if a manufacturer knows or has knowledge of facts that would give him notice, that a drug 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 drug which accords with such other uses to which the article is to be put~~.

Unapproved Use

FDA's Ban on Off-Label Promotion

FDA's longstanding position is that a manufacturer who promotes an approved drug for an unapproved use violates the Act—regardless of the drug's safety and efficacy for the off-label use

According to FDA, off-label promotion violates the FD&C Act

- Misbranding
- Unapproved new drug

Unapproved Use

FDA's Rationale for prohibiting off-label promotion

- Causes healthcare providers to avoid or delay using known, effective therapies in favor of unapproved products
- Blurs the distinction between investigational and approved products
- Undermines the integrity of drug and device approval processes

Practice of Medicine

FDA does not regulate the "Practice of Medicine"

Physicians may use an approved drug for an off-label use

- In some specialties (e.g., oncology), off-label use of drugs is the medically recognized standard of care

Physicians must be careful about promoting a drug for off-label use

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First Amendment Jurisprudence

First Amendment

"Congress shall make no law . . . abridging the freedom of speech . . . ."

History of Tension Between FDA's Off-Label Framework and the First Amendment

Kefauver-Harris Amendments of 1962

- Required a showing of safety and efficacy for each new intended use prior to marketing

"Intended Use" Regulation (Feb. 1976)

- Speech/circumstances of persons responsible for the labeling of the article may be evidence of a "new intended use"

Virginia State Bd. of Pharmacy v. Virginia Cit. Cons. Council (May 1976)

- "Commercial speech" not wholly outside of the First Amendment
- Statutory ban on advertising prescription drug prices violated First Amendment

Commercial Speech

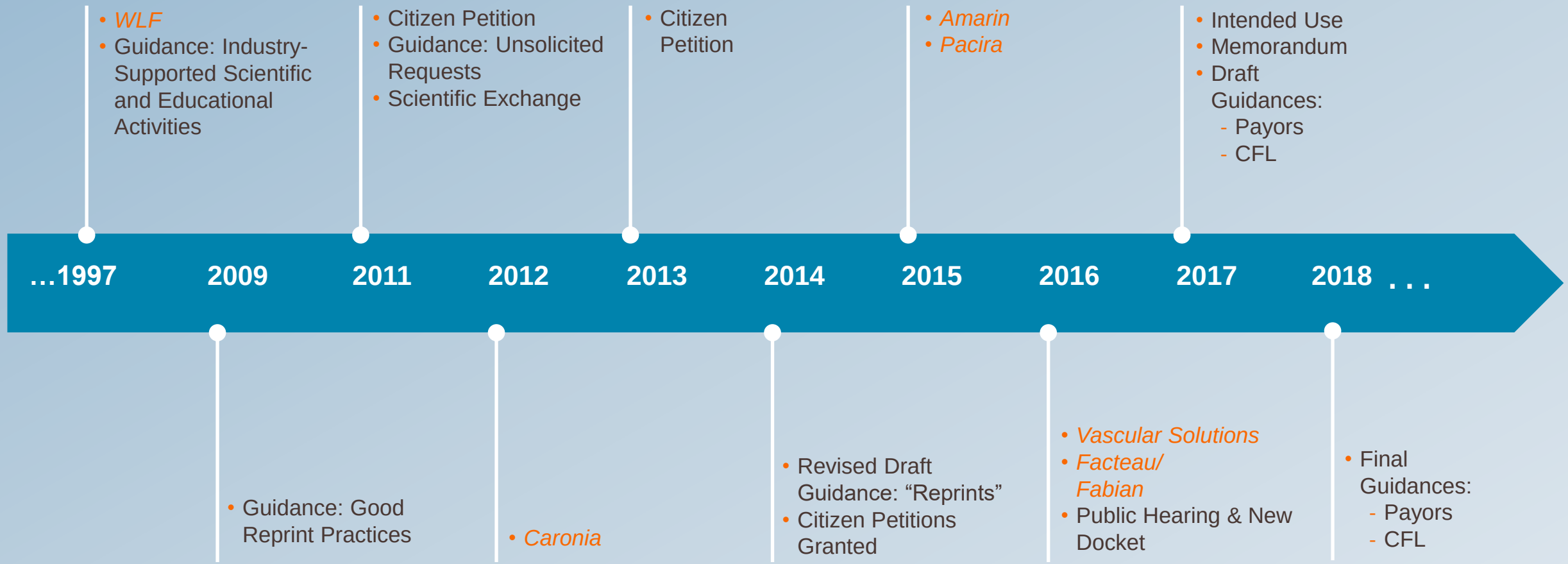
Commercial speech enjoys First Amendment protection

Restrictions on commercial speech evaluated under four-part *Central Hudson* test

1) Does the speech concern lawful activity and is not misleading?
2) Is the government's interest substantial?
3) Does the restriction directly and materially advance the government's interest?
4) Is the restriction narrowly tailored?

Central Hudson Gas & Electric Corp. v. Public Service Commission of New York, 447 U.S. 557, 100 S.Ct. 2343, 65 L.Ed.2d 341 (1980).

Evolution of FDA First Amendment Policy



Washington Legal Foundation v. Friedman

1994

WLF sues FDA

First Amendment challenge to FDA guidances on industry-supported scientific and educational activities

Guidances restricted manufacturers' ability to discuss off-label uses with the medical community

1998

D.D.C. (Judge Lamberth) recognizes a First Amendment right to disseminate off-label information

Holds FDA guidance unconstitutional

Permits FDA to impose some restrictions on dissemination of off-label information

Washington Legal Foundation v. Henney

1997

Congress enacts FDAMA

1998

WLF sues FDA: First Amendment challenge to section 401 of FDAMA

FDAMA 401 limited dissemination of off-label information

1999

Judge Lamberth finds that restrictions in section 401 of FDAMA violated the First Amendment

Appeal of WLF Cases

2000

WLF cases mooted on appeal

FDA claims for the first time that FDA guidances and section 401 of FDAMA are a "safe harbor"

D.C. Circuit vacates Judge Lamberth's rulings - "not criticiz[ing] the reasoning or conclusions of the district court"

Post WLF

FDA reverted to its longstanding practice of regulating off-label promotion through case-by-case enforcement action

United States v. Caronia

Apr. 2006

Government (E.D.N.Y.) indicts Orphan Medical, Alfred Caronia, David Tucker, and Dr. Peter Gleason

Alleges off-label promotion of Xyrem

Mar. 2007

Tucker pleads guilty

July 2007

Orphan pleads guilty

- $20 million
- CIA

Aug. 2008

Dr. Gleason pleads guilty

United States v. Caronia

November 2009—Caronia goes to trial and is convicted of misbranding based on off-label statements to HCPs

- Appeals based on First Amendment defense

December 2012—Second Circuit reverses

- Holds that FD&C Act's misbranding provision does not prohibit/criminalize "the truthful off-label promotion of FDA-approved prescription drugs"
- FDA's interpretation of the FD&C Act's misbranding provision is not sustainable under *Central Hudson*
  - Speech in question was about a lawful activity and was not false or misleading
  - FDA has substantial interest in drug safety and public health, but prohibition of off-label promotion does not directly advance that interest
  - Complete criminal ban on off-label promotion is not narrowly tailored

First Amendment Summary

Speech Must Be Truthful and Not Misleading

The First Amendment only protects speech that is truthful and non-misleading

- Courts will closely scrutinize company's off-label claims to ensure they are not false or misleading
- Science evolves, so something that is truthful today might become false tomorrow

What is "misleading" is not easily defined

- Even minor deviations in claims can cause them to be misleading, meaning they are not protected by the First Amendment

First Amendment Summary

Off-Label Promotion Remains High Risk

Tread cautiously when moving into "unapproved use" territory

The government may continue to pursue off-label promotion cases against companies and individuals

First Amendment protection only applies to speech that is both truthful and non-misleading

- *Amarin*: "A manufacturer that leaves its sales force at liberty to converse unscripted with doctors about off-label use of an approved drug invites a misbranding action if false or misleading (e.g., one-sided or incomplete) representations result."

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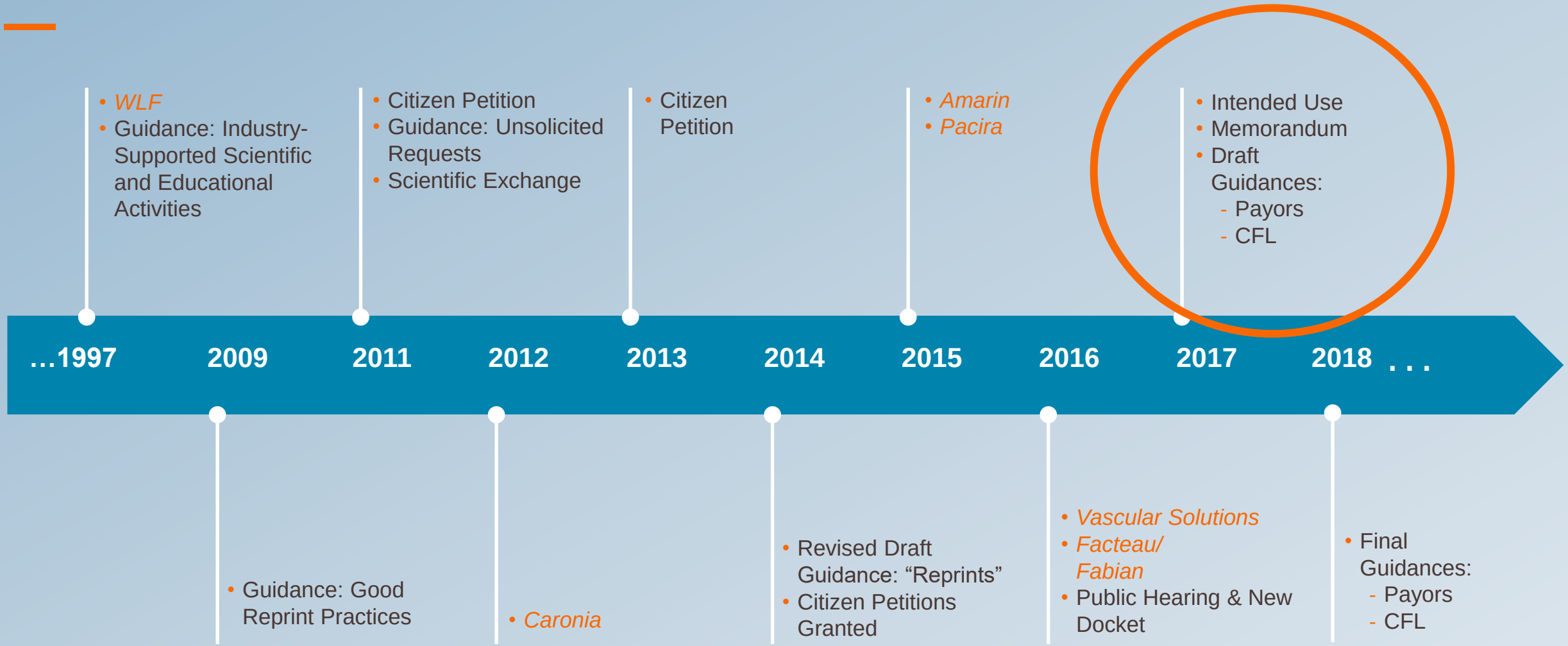
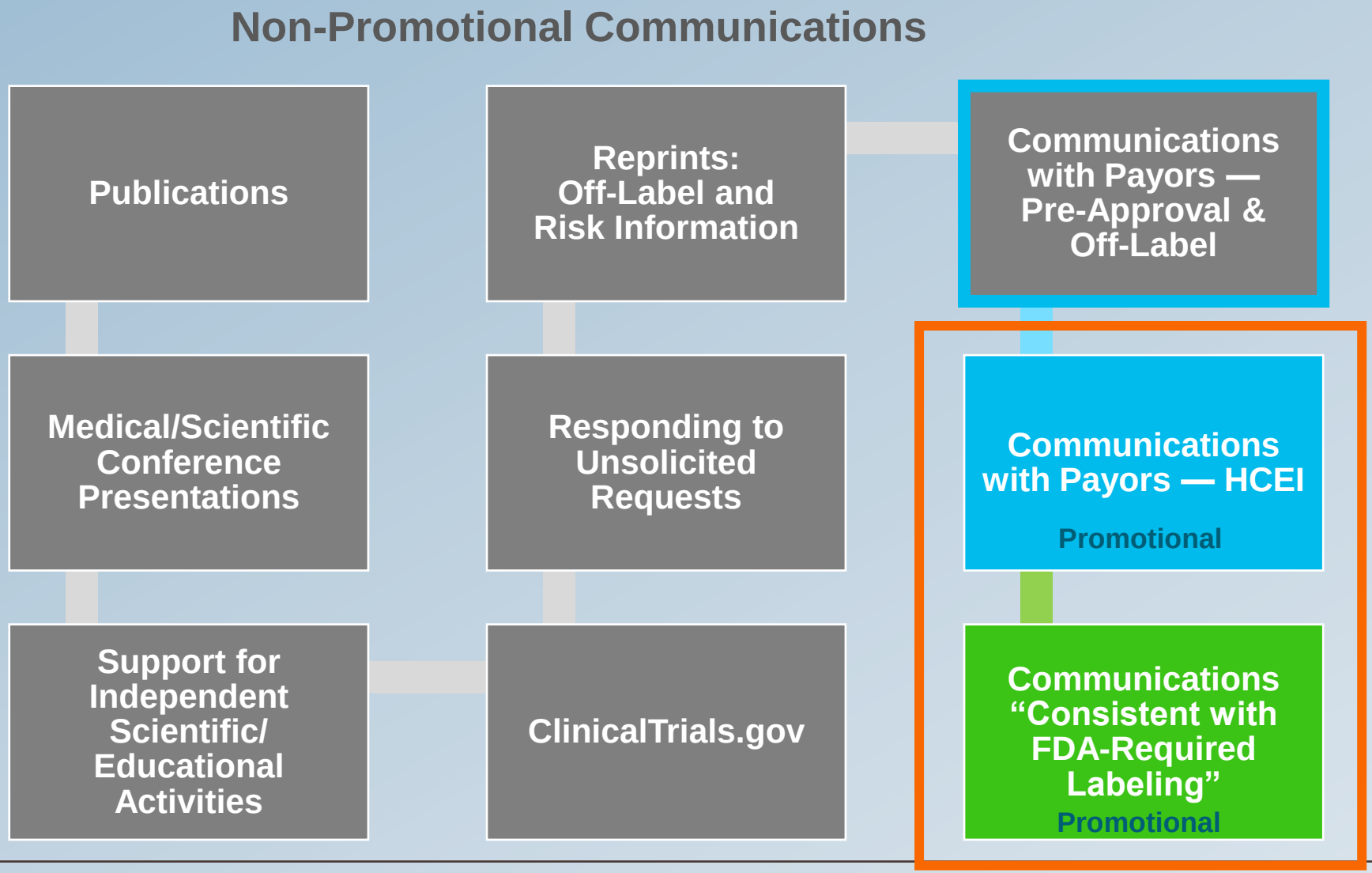
FDA Guidance

Evolution of FDA First Amendment Policy



Expanded Communication Pathways Over Time



CFL Communications

Communications That Are Consistent With FDA-Required Labeling

Guidance for Industry: Medical Product Communications That Are Consistent With the FDA-Required Labeling — Questions and Answers (June 2018)

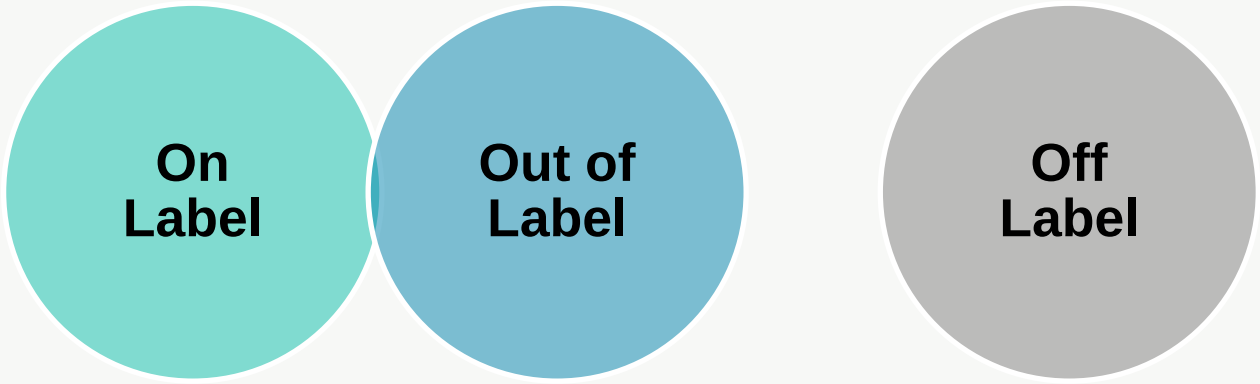
CFL Guidance

Describes how FDA intends to treat promotional communications that are:

- Not contained in FDA-required labeling, but
- Consistent with FDA-required labeling

Information will not be considered evidence of a new intended use or failure to provide adequate directions for use

"Alternative approach" may be used if it satisfies applicable legal requirements



CFL Guidance

Three-Factor Test

How does the "out of label" information compare to the FDA-required labeling?

- Indication
- Patient Population
- Limitations and Directions for Handling/Use
- Dosing or Use Regimen/Administration

Does the "out of label" information increase the potential for health risks relative to information in the FDA-required labeling?

Does the FDA-required labeling enable the product to be safely and effectively used under conditions suggested by the "out of label" information?

CFL Three-Factor Test

Factor Overlap and Examples

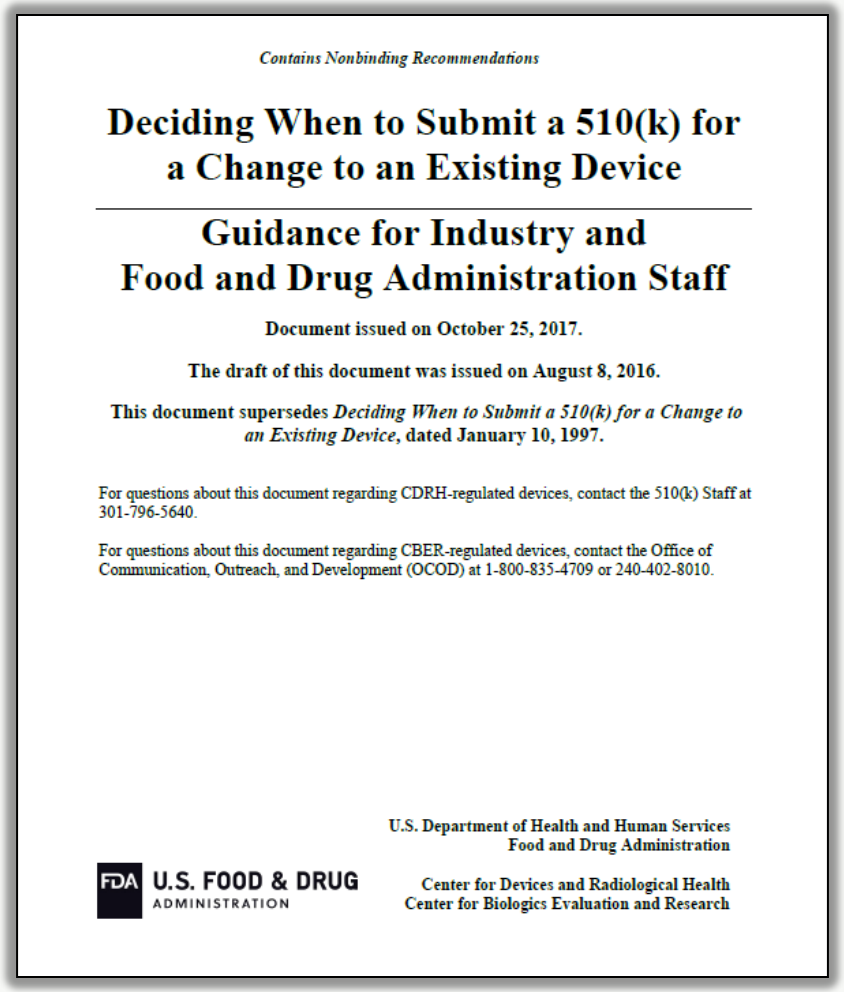
- FDA recognizes that there is overlap in factors and communications may fail more than one test factor
- Examples: Factor 1 (primarily addresses conflict) vs Factors 2 and 3
  - Switching
    - Switching between Drug A and Drug B, where Drug A's PI requires a washout period before treatment with another product. Drug B's switching communication passes Factor 1, but fails Factors 2 and 3
  - Dose modification
    - PI recommends dose modifications necessary for individual safety and tolerability, but does not provide specifics. Communication that provides specific dose modification creates sub-therapeutic dose. Communication passes Factor 1, but fails Factor 3

CFL Three Factor Test — Scope

510(k) Cleared and Exempt Devices

Devices that are cleared in 510(k)s and devices that are 510(k) exempt

- No separate analysis under Three Factor Test
- Conduct analysis of communication under:
  - 21 C.F.R. § 807.81(a)(3) and
  - Guidance for Industry and FDA Staff, Deciding When to Submit a 510(k) for a Change to an Existing Device (October 2017)



Contains Nonbinding Recommendations

Deciding When to Submit a 510(k) for a Change to an Existing Device

Guidance for Industry and Food and Drug Administration Staff

Document issued on October 25, 2017.

The draft of this document was issued on August 8, 2016.

This document supersedes *Deciding When to Submit a 510(k) for a Change to an Existing Device*, dated January 10, 1997.

For questions about this document regarding CDRH-regulated devices, contact the 510(k) Staff at 301-796-5640.

For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach, and Development (OCOD) at 1-800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration

FDA U.S. FOOD & DRUG ADMINISTRATION

Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

CFL Examples

- Comparisons
- Adverse Reactions
- Onset of Action
- Long-term safety/efficacy
- Patient Subgroups
- Product Effects
- Convenience
- Mechanism of Action
- Tolerability with concomitant use in co-morbid condition

CFL Substantiation Standard

"Scientifically Appropriate and Statistically Sound"

Must be truthful and not misleading

- "When communications lack appropriate evidentiary support, they are likely to be false or misleading and can cause patient harm." (CFL Guidance Q.6./A.6.)

Does not require "substantial evidence"

Claim-by-claim analysis

Amount and type of evidence depends on

- Topic of communication (e.g., long term efficacy vs MOA)
- Particular representations/suggestions made about topic

Truthful and Not Misleading — Other CFL Considerations

Contextual information (including disclosures) is critical

Do not overstate findings or conclusions from studies/analyses

- If data are inadequate to support the claim, disclosures cannot cure the misleading message

Clearly and Prominently Disclose

- Underlying study results, data and information
- Material aspects and limitations of the study design and methodology (e.g., type of study, study objectives, drug dosage/use regimens, controls used, patient population studied, and outcome measures)
- Material limitations of data (e.g., factors that can affect interpretability and reliability of the data, such as limitations of the data sources)
- Unfavorable or inconsistent findings
- Information from FDA-required labeling to help contextualize the communication

Communications with Payors – HCEI

Guidance for Industry and Review Staff: Drug and Device Manufacturer Communications with Payors, Formulary Committees, and Similar Entities — Questions and Answers (June 2018)

Previous HCEI Framework – FDAMA 114

FDCA § 502(a) (as amended by FDAMA)

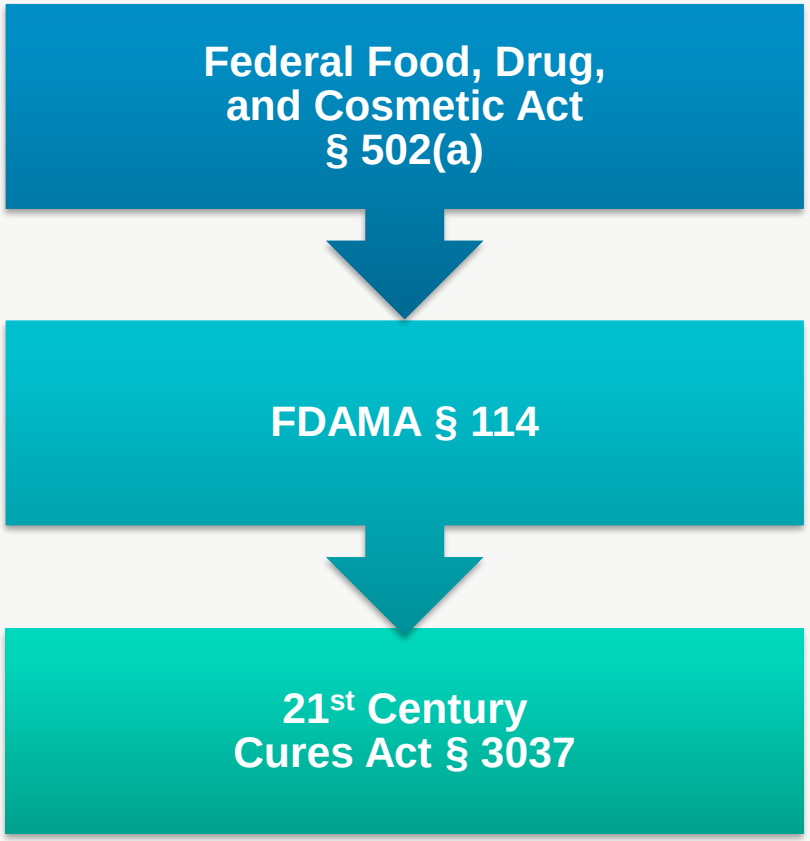
A drug or device shall be deemed to be misbranded—

(a) False or misleading label

If its labeling is false or misleading in any particular. Health care economic information provided to a formulary committee, or other similar entity, in the course of the committee or the entity carrying out its responsibilities for the selection of drugs for managed care or other similar organizations, shall not be considered to be false or misleading under this paragraph if the health care economic information directly relates to an indication approved under section 355 of this title or under section 262 (a) of title 42 for such drug and is based on competent and reliable scientific evidence. The requirements set forth

Communications with Payors — HCEI

Health Care Economic Information (HCEI)



New HCEI Framework

- Expands HCEI beyond economic "analysis"
- Includes comparative analyses to another drug or intervention
- Clarifies covered audience
- HCEI "relates to" an approved indication
- Based on competent and reliable scientific evidence (CARSE)

HCEI Communications with Payors — Scope

HCEI Communications to Payors Regarding Approved Drugs

HCEI Communications to Payors Regarding Approved/Cleared Devices

Communications with Payors — HCEI

HCEI

- "clinical data, inputs, clinical or other assumptions, methods, results and other components underlying or comprising the analysis"
- Variety of formats (e.g., evidence dossier, reprint)

Audience

- Healthcare decision maker
- Consider HCEI through a "deliberative process"
- "Appropriate range of knowledge and expertise in … HCEI"
- **Not an HCP *unless* multiple roles**

Promotional

- Proactive HCEI is considered promotion
- Drugs: Post-marketing reporting via Form FDA 2253

"Relates to"

- *Relates to* "the disease or condition, the manifestation of the disease or condition, or symptoms associated with the disease or condition in the patient population for which the drug is [approved]."

CARSE

- "Generally-accepted scientific standards, appropriate for the information being conveyed, that yield accurate and reliable results."
- Authoritative bodies' standards

Context

- Study design
- Methodology
- Generalizability
- Limitations
- Sensitivity analyses

Examples – HCEI "Related to" Approved Indication

- Duration of Treatment
- Health Care Setting
- Burden of Illness
- Dosing/ Use Regimen
- Patient Subgroups
- Length of Hospital Stay
- Surrogate or Intermediate Endpoints
- Clinical Outcome Assessments or Other Health Outcome Measures
- Compliance/ Adherence
- Persistence
- Comparisons

HCEI Substantiation Standard

"Competent and Reliable Scientific Evidence" (CARSE)

"Generally-accepted scientific standards, appropriate for the information being conveyed, that yield accurate and reliable results."

Consider standards and good research practices developed by other authoritative bodies

- Examples: International Society for Pharmacoeconomic and Outcomes Research (ISPOR), International Society for Pharmacoepidemiology (ISPE), Agency for Healthcare Research and Quality (AHRQ)

Truthful and Not Misleading — Contextual Considerations

Contextual information (including disclosures) is critical

Acknowledgement that contextual information may be burdensome

Examples that may — or may not — be applicable to particular HCEI presentations

Study Design & Methodology	Generalizability	Limitations	Sensitivity Analysis
• Type of Analysis • Modeling • Patient Population • Perspective/Viewpoint • Comparator • Time Horizon • Outcome Measures • Cost Estimates • Assumptions	• Applicability of HCEI obtained in one healthcare setting or patient population to another	• Factors that may affect interpretability and reliability	• Address uncertainty from data sources, extrapolation, or analytical methods

Truthful and Not Misleading — Contextual Considerations

Additional Material Information for a Balanced and Complete Presentation

- **Conspicuous and Prominent Statement Describing Material Differences**
- **FDA-Approved Indication/FDA-Approved Labeling**
- **Disclosure of Omitted Studies or Data Sources**
- **Risk Information**
- **Financial/Affiliation Biases**

Non-Promotional Communications

Types of communications, if delivered in a manner consistent with FDA guidance, that are not typically considered to be promotional

Scientific Exchange

- Scientific Presentations & Publications
- Independent Scientific & Educational Activities
- Responses to Unsolicited Requests
- Reprints
- ClinicalTrials.gov
- Payor Communications regarding Unapproved Drugs & Uses

"Internal" Communications

- Consultants
- Advisory Boards
- Market Research
- Clinical Investigators

Other (External) Communications

- Investor Communications
- Corporate Communications
- Disease Awareness
- Clinical Trial Recruiting
- Correcting Misinformation

Scientific Exchange

FDA restricts a broad range of company communications about its products via FDA's authority to

- Prohibit false and misleading claims
- Prohibit unapproved new drugs (or new intended uses of approved drugs)
- Prohibit preapproval promotion of investigational drugs

Although FDA does not restrict the free exchange of scientific information concerning a drug, including the dissemination of scientific findings in scientific or lay media, this is **a narrow and highly scrutinized carve out**

Non-Promotional Communications Guidance

Support of Independent Education	• Industry-Supported Scientific and Educational Activities
Disseminating Scientific & Medical Publications*	• Good Reprint Practices • Distributing Scientific and Medical Publications on Unapproved New Uses • Distributing Scientific and Medical Publications on Risk Information for Approved Products
Responding to Unsolicited Requests*	• Responding to Unsolicited Requests for Off-Label Information
Communications with Payors	• Communications with Payors, Formulary Committees, and Similar Entities (Unapproved Products and Uses)
Correcting Misinformation*	• Internet/Social Media Platforms: Correcting Independent Third-Party Misinformation

*FDA Guidance restricts safe harbors to approved products

Hallmarks of Product-Related Non-Promotional Communications

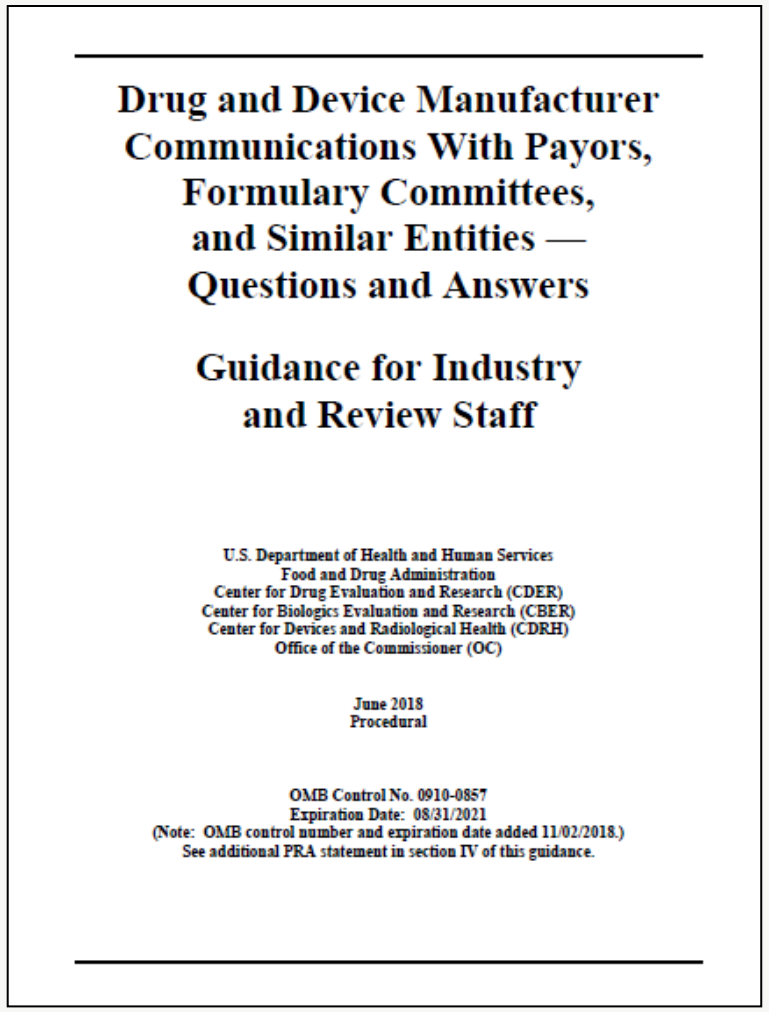
Expected to be a balanced, unbiased, straightforward presentation of the data in context

1) Clearly discloses the investigational status of the drug
2) Makes no claims (express or implied) of safety or efficacy
3) Contains only information that is truthful and not misleading when measured against available information on the drug
4) Non-promotional in manner and tone

Communications with Payors – Pre-Approval and Unapproved Uses

Guidance for Industry and Review Staff: Drug and Device Manufacturer Communications with Payors, Formulary Committees, and Similar Entities — Questions and Answers (June 2018)

New Safe Harbor: Payors



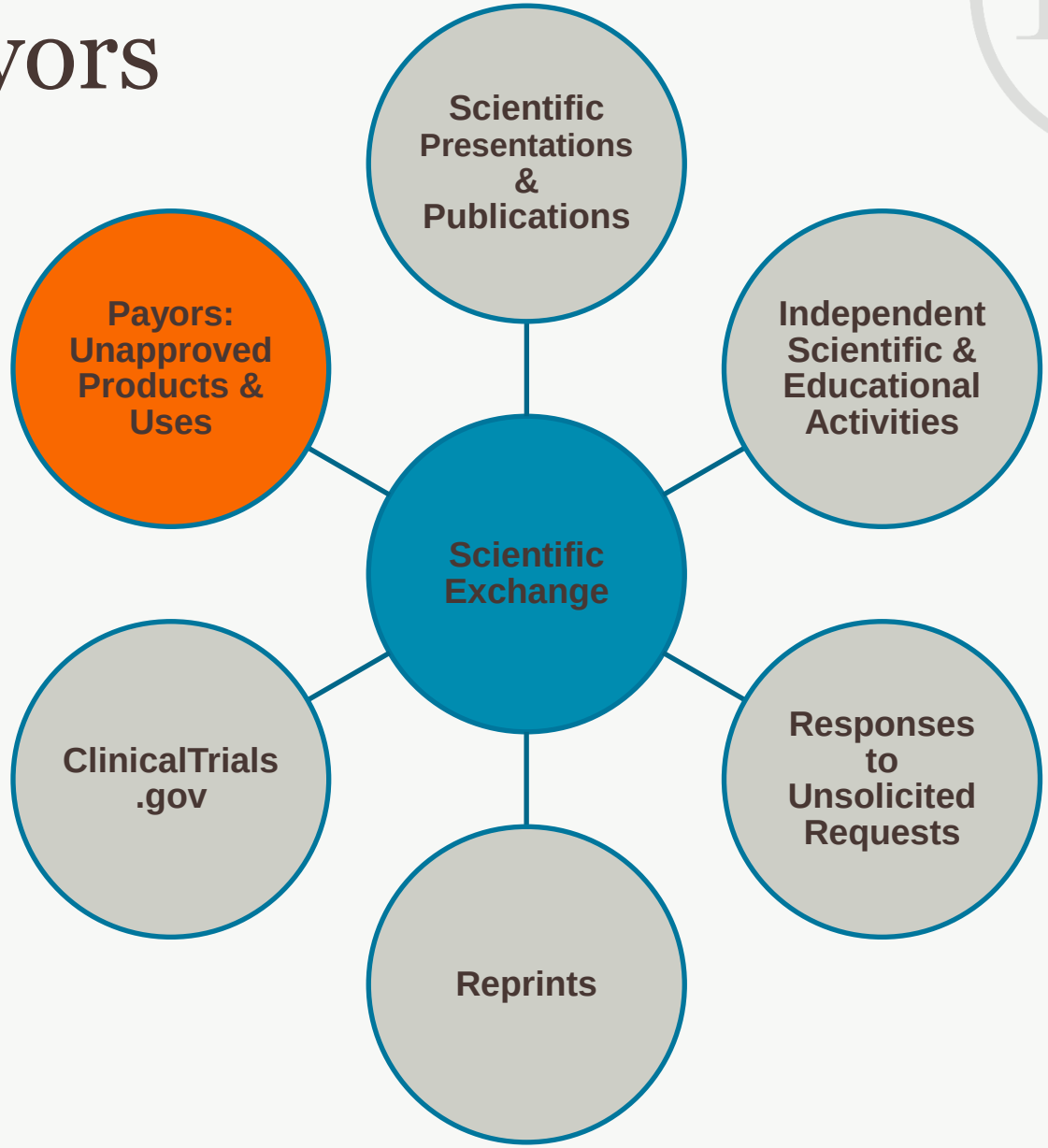
Drug and Device Manufacturer Communications With Payors, Formulary Committees, and Similar Entities — Questions and Answers

Guidance for Industry and Review Staff

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Office of the Commissioner (OC)

June 2018
Procedural

OMB Control No. 0910-0857
Expiration Date: 08/31/2021
(Note: OMB control number and expiration date added 11/02/2018.)
See additional PRA statement in section IV of this guidance.



Communications with Payors

Unapproved Products and Uses "Safe Harbor"

Expressly permits pre-approval communications with payors

- Unapproved products (drugs and devices) that are not yet approved/cleared by FDA for any use, including products for which a firm has submitted or plans to submit a marketing application (NDA, BLA, ANDA, PMA, 510(k), de novo submission, or HDE)

Expressly permits off-label communications with payors

- Unapproved uses of approved/cleared/licensed products (drugs and devices)
- Query pre-approval status (i.e., pending or planned marketing application)?

No recommendation on timing/when to engage payors

"Unbiased, factual, accurate, and non-misleading" and non-promotional

- Must consider appropriate disclosures about product status, stage of development, study design and limitations

Communications with Payors

Unapproved Products and Uses "Safe Harbor"

SCOPE OF PERMISSIBLE INFORMATION

- **Product Information** (e.g., drug class, device description)
- **Proposed Indication(s)**
- **Factual Presentations of Study Results**
- **Pricing Information**
- **Patient Utilization Projections**
- **Product-Related Programs or Services**
- **Anticipated Timeline for Approval/ Clearance**
- ~~**Marketing Strategies**~~ *Removed in Final Guidance*

Disclosures and Contextual Considerations

Contextual information (including disclosures) is critical

Ensure unbiased, factual, accurate, and non-misleading information

Disclosures

- Clear statement that product is not approved/cleared/licensed and that safety/effectiveness has not been established
- Stage of development
- Material aspects of study design/methodology and disclose material limitations for any factual presentations of study results
- For unapproved uses of approved/cleared/licensed products
  - Add a prominent disclosure of approved/cleared/licensed indication
  - Include a copy of FDA-required labeling

"Reprints" – Disseminating Scientific & Medical Publications

Guidance for Industry: 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 (January 2009)

Revised Draft Guidance for Industry: Distributing Scientific and Medical Publications on Unapproved New Uses — Recommended Practices (February 2014)

Draft Guidance for Industry: Distributing Scientific and Medical Publications on Risk Information for Approved Prescription Drugs and Biological Products—Recommended Practices (June 2014)

Medical and Scientific Publications: "Reprints"

Reprints generally treated as promotional labeling and must meet labeling requirements, including prohibitions against off-label promotion

"Safe harbor" exception for reprints involving off-label use(s) if disseminated in accordance with all conditions of FDA's guidance documents

Off-label reprints not disseminated in full compliance with guidance are not necessarily violative, but can invite objection

Off-Label Reprints: Safe Harbor

FDA Draft Guidance (February 2014) applies to scientific or medical information on the safety and effectiveness of an **approved drug for an unapproved "new use"** that is not included in the product's labeling

- Applicable to distribution to formularies and benefits managers, as well as physicians and hospitals
- Includes guidance for distribution of
  - Scientific/medical journal articles
  - Scientific/medical reference texts
  - Clinical Practice Guidelines

Reprints – Distribution Considerations

Scientific publications should be:

- Peer-reviewed
- In the form of an unabridged reprint or copy of an article (i.e., no marking, highlighting or summary)
  - Prohibition on marking / highlighting encompasses both written and oral statements made by, or on behalf of, the manufacturer
- Based on 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

Reprints – Distribution Considerations

Scientific publications should be:

- Disseminated with:
  - FDA-approved labeling for the product
  - A comprehensive bibliography, when such information exists
  - Representative publications that reach contrary or different conclusions
- Distributed separately from promotional information (i.e., no distribution in promotional exhibit halls or during promotional speakers programs)

Reprints – Distribution Considerations

Scientific publications should be:

- Accompanied by appropriate disclosures – prominently displayed and permanently affixed
  - The drug(s) or device(s) included in the journal reprint in which the manufacturer has an interest
  - Uses of the drugs or devices described in the reprint have not been approved or cleared by FDA
  - Financial conflicts of authors
  - Any person known to the manufacturer who has provided funding for the study
  - All significant risks or safety concerns associated with the unapproved use(s) of the manufacturer's product(s) discussed in the journal article that are known to the manufacturer but not discussed in the article

Reprints – Distribution Considerations

Scientific publications must not:

- Be false or misleading
  - e.g., an article should not discuss a clinical investigation that FDA has previously informed the company is not adequate and well-controlled
- Contain information recommending or suggesting use of the product that makes the product dangerous to health when used in the manner suggested
- Be an excluded category
  - 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

Medical and Scientific Publications: Risk Information Reprints

New risk information

Reprints about information that becomes available after a drug is marketed that

- Rebuts or mitigates information about a risk already identified in the approved labeling
- Otherwise refines risk information in the approved labeling in a way that does not indicate greater seriousness of the risk

Examples:

- Severity or rate of occurrence of an AE is lower than described in the approved labeling
- Data calls into question a causal relationship between a drug and an AE in the approved labeling
- Risks in a subpopulation

Medical and Scientific Publications: Risk Information Reprints

Data Source Guidelines

- ✓ Study or analysis should meet accepted design and other methodologic standards
- ✓ Study or analysis should also be at least as persuasive as the data sources that underlie the existing risk assessment
- ✓ Conclusions should give appropriate weight, consideration, and fair characterization of, all relevant safety information, including inconsistent findings
- ✓ Published in an independent, peer-reviewed journal

Medical and Scientific Publications: Risk Information Reprints

Distribution Guidelines

- ✓ Cover sheet disclosures
  - Study design, critical findings, and significant methodologic or other limitations
  - Information is not consistent with certain risk information in the approved labeling
  - FDA has not reviewed the data
  - Financial interests or affiliations of study authors and manufacturer
- ✓ Accompanied by the approved labeling
- ✓ Separate from promotional material
- ✓ Any oral statements must be consistent with its content and the information in the disclosure cover sheet

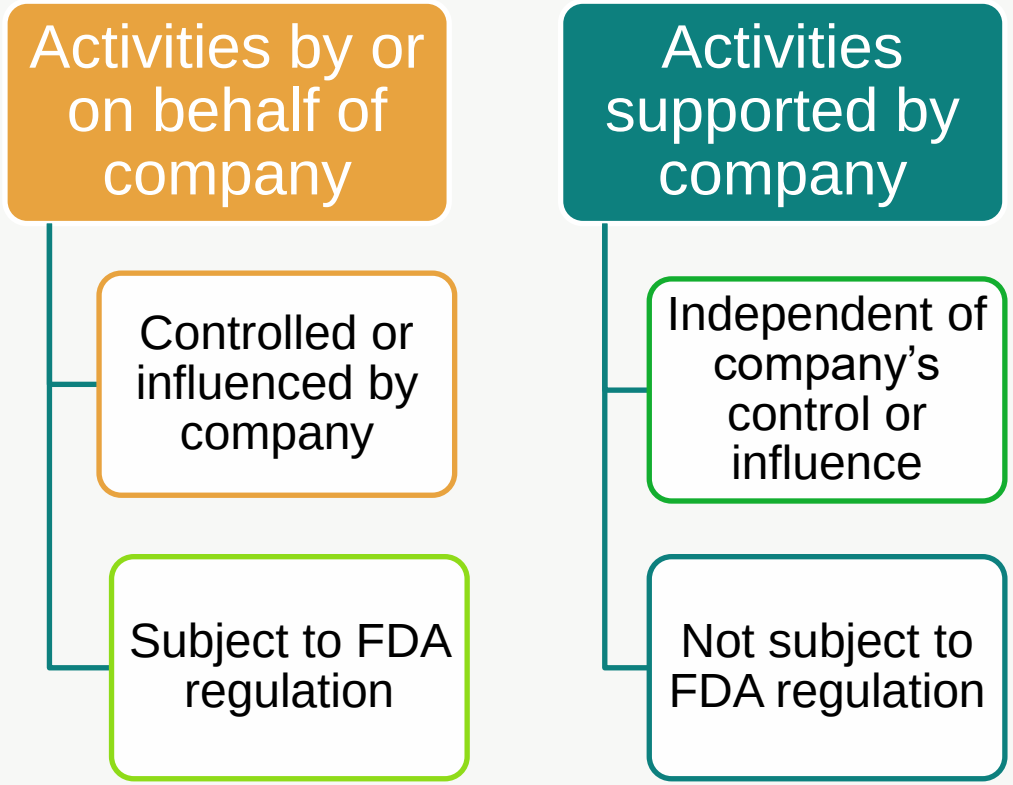
Support for Independent Scientific & Educational Activities

Guidance for Industry: Industry-Supported Scientific and Educational Activities (November 1997)

ACCME Standards for Commercial Support: Standards to Ensure the Independence of CME Activities (2004, 2005, 2014)

Industry-Supported Activities

Promotion, Education, and Independence



Industry-Supported Activities

Factors for Evaluating Independence

Control of content / Selection of speakers	Disclosures (e.g., financial interest, unapproved use)	Program Focus	Relationship between provider and sponsor
Provider involvement in sales/marketing	Provider performance/demonstrated failure	Multiple presentations	Audience selection
Opportunities for discussion	Dissemination	Ancillary promotional activities	Complaints

Responding to Unsolicited Requests

Draft Guidance for Industry: Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices (December 2011)

Responding to Off-Label Inquiries

Establishes a “safe harbor” for off-label information

Companies may respond to unsolicited questions about off-label uses without being deemed to promote those uses

- Unsolicited requests are initiated by persons or entities that are completely independent of the firm
- Companies must not solicit (i.e., prompt or encourage) healthcare practitioners to request off-label information

Distinguishing Solicited from Unsolicited Requests

Examples of *solicited* requests for off-label information

- Presentation of off-label data by paid speakers including a “medical science liaison” or “key opinion leader” at a company-sponsored promotional event
- Promotional pieces that cite clinical studies of off-label conditions, or commercial exhibits announcing new uses for products (e.g., “Coming Soon, a new use for Product X”)
- Provision of URLs that implicate off-label information
- Encouragement of users to post testimonials or videos (e.g., on YouTube)
- Communications that provoke discussions of off-label use on blogs, whether posted as comments to a third-party site or directed to the firm

Publicly Responding to Unsolicited Requests: "Safe Harbor"

Public unsolicited requests are requests made in any public forum (e.g., meetings, Web-based 3rd party discussion forum)

Company should respond only if public request pertains specifically to its own named product

Publicly Responding to Unsolicited Requests: "Safe Harbor"

Public response should be limited to:

- A statement that the question pertains to unapproved/uncleared use of the product
- Contact information for the medical or scientific department to obtain more information
- A disclosure of the responder's involvement with the company
- A mechanism for accessing the FDA-approved product labeling

Public response should not:

- Include off-label information
- Be promotional in nature/tone

Providing Off-Label Information in Response to Unsolicited Requests: "Safe Harbor"

Response Should Be

- ✓ Private (provided only to the requesting individual)
- ✓ Narrowly tailored to the request
- ✓ Truthful, non-misleading, accurate, balanced, and scientific
- ✓ Not promotional or accompanied by promotional material
- ✓ Prepared by medical/scientific (not sales) personnel
- ✓ Documented

Response Should Include

- ✓ Copy of FDA-required labeling
- ✓ Statement that FDA has not approved or cleared the product as safe or effective for the use addressed in the materials provided
- ✓ Disclosure of the approved or cleared indications of the product
- ✓ List of references for all information provided in the response
- ✓ Statement providing important safety information for the product

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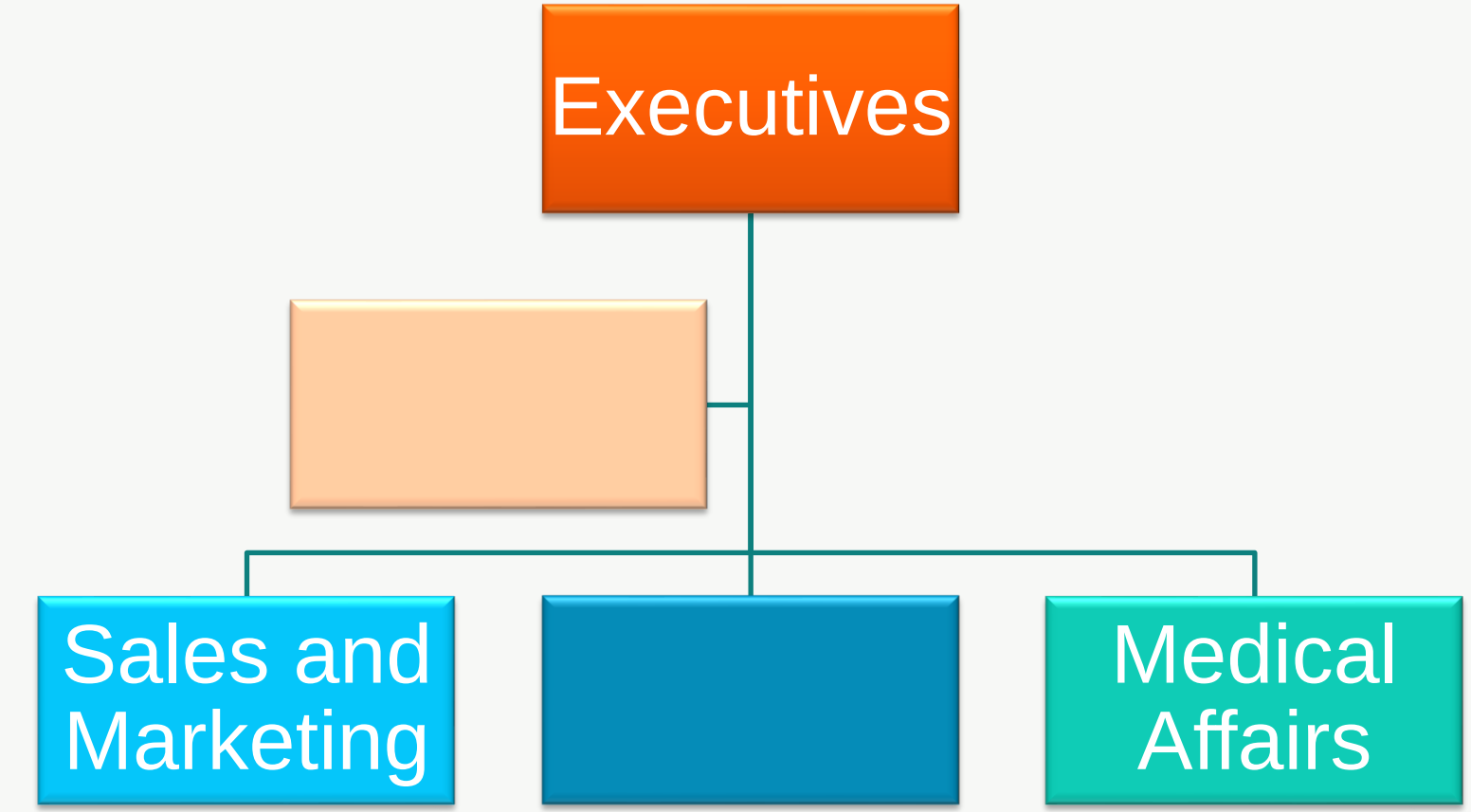
Role of Medical Science Liaisons

Clear Separation of Functions



Why Medical Activities Should Differ from Sales Activities

Non-Promotional vs Promotional Roles

If a separation between Medical and Sales/Marketing is not maintained, the government may view Medical in the same manner as Sales/Marketing

- Commingling the functions can taint these otherwise legitimate Medical Affairs activities and communications
- With the lines blurred, the government may then consider Medical's conduct of scientific exchange related to unapproved uses or products to be unlawful off-label promotion
- FDA calls this "white coat marketing"

FDA Statements About MSLs

OPDP has publicly cautioned companies that there is no difference between MSLs and commercial/sales personnel

"FDA holds the medical affairs department to the same standards as it does sales reps. It's important to keep from blurring the lines between promotion and responses to unsolicited requests."

"Just because you have a person with a different hat in a different booth, if they are promoting a drug [providing off-label information is still] against the law."

Thomas Abrams, Director of FDA's Office of Prescription Drug Promotion (OPDP)

Potential Roles of MSLs

- Discuss appropriate scientific and medical information with healthcare professionals (HCPs)
- Engage in scientific and educational communications at medical meetings
- Staff scientific, not promotional, booths at national and regional medical conferences
- Support clinical and educational initiatives
- Respond to unsolicited requests for off-label information
- Conduct speaker and sales force training on medical or scientific issues within appropriate limits
- Develop and manage relationships with KOLs and investigators
- Discuss risks, benefits, and full prescribing information associated with a product when engaging in product discussions
- Educate customers about disease states

Preserve the Ability to Execute Non-Promotional Activities

The more Medical engages in promotional activities, the harder it becomes to defend its non-promotional activities. Consider:

- Whether non-promotional Medical activities appear to be influenced or driven by Commercial objectives
- Whether it appears that Sales personnel are directing Medical personnel on non-promotional activities
- How Medical participates in strategic discussions regarding increasing sales, relationships or commercial opportunities
- Whether Commercial views Medical non-promotional activities as a mechanism for increasing sales, relationships or commercial opportunities

Questions?

Dissemination of Information About Unapproved Uses

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- Focuses on regulatory strategies and initiatives for the labeling, advertising and promotion of FDA-regulated products
- Serves as a legal and/or regulatory member on promotional and medical/scientific review committees
- Over 20 years of experience in FDA law at major law firms, in government, and in-house

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