Introduction to Advertising and Promotion: Applicable FDA Offices, Essential Principles, and Key Definitions

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October 12, 2021

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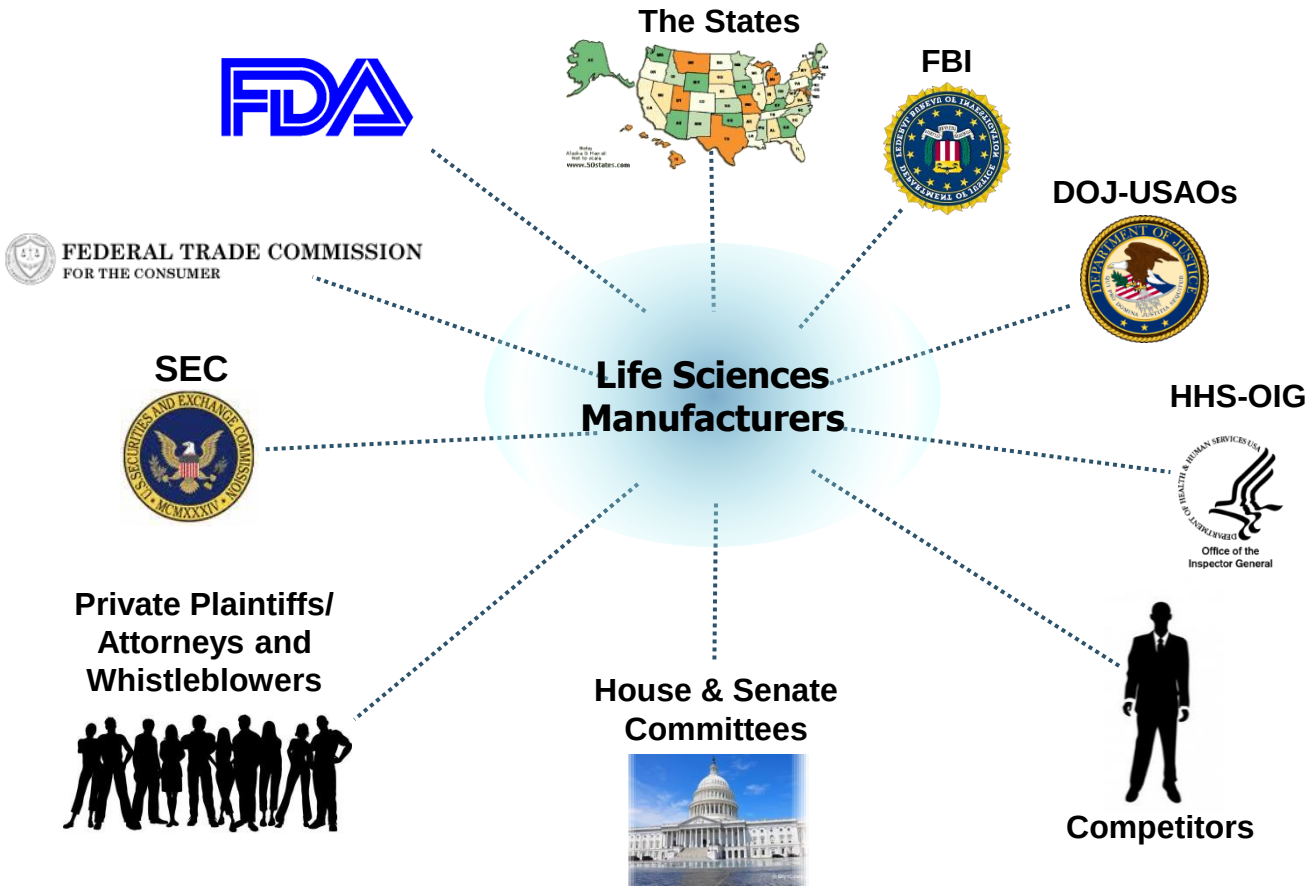
Agenda

- **Why it Matters**
- **FDA Offices**
- **FDA Enforcement**
- **Key Definitions and Essential Principles of Advertising and Promotional Labeling**
- **Types of Claims**
- **Traditional and Other Forums**
- **Preapproval Communications**
- **Submissions**

Why it Matters

Stakeholders



Laws and Evidence

First Amendment		
FDCA FDA Regulations Guidance Documents	FTC Act	Lanham Act
Substantial Evidence	SASS	CARSE	"Reasonable Consumer" Standard; Substantiation	Literally false OR true but likely to mislead

FDA Law

- **Federal Food, Drug, and Cosmetic Act** (FD&C Act or FDCA), codified at 21 U.S.C.
- **Public Health Service Act** (PHSA)
- **FDA Regulations**, 21 C.F.R.
- **FDA Guidance**
- Other laws related to FDA action:
  - Federal fraud and abuse laws (e.g., Anti-Kickback Statute, False Claims Act)
  - Lanham Act (e.g., competitor suits)
  - State statutes (e.g., consumer protection; product liability)

FDA Offices

FDA Offices

- CDER Office of Prescription Drug Promotion (OPDP)
- CBER Advertising and Promotional Labeling Branch (APLB)
- CDRH Division of Premarket and Labeling Compliance (DPLC)

FDA Enforcement

FDA Enforcement Tools

- FDA enforcement tools
  - Warning Letters
  - Untitled Letters: do not meet the threshold of regulatory significance for a Warning Letter
  - Referrals to other federal agencies (e.g., SEC, DOJ, FTC)

FDA's Bad Ad Program

- FDA's Bad Ad Program
  - Outreach program for healthcare professionals
  - HCPs can report misleading promotion to FDA (BadAd@fda.gov)

Key Definitions and Essential Principles of Advertising and Promotional Labeling

Intended Use and New Drug Approval Requirement

- "**Intended use**" refer to the "**objective intent"** of the person responsible for the labeling. Intent shown by

  "such persons' expressions, the design or composition of the article, or by the circumstances surrounding the distribution of the article. ... for example, … by **labeling claims, advertising matter**, or oral or written statements by such persons or their representatives. …"

  21 C.F.R. § 201.128; 21 C.F.R. § 801.4

- Intended use determines whether a product's advertisement or labeling is off label
- Mere knowledge that an approved drug is prescribed or used off label does not constituent intended use for such use

Substantial Evidence

- **Substantial evidence: standard for approval of a new intended use for a drug**
- Section 505(d) of the Act defines "substantial evidence," which consists of "adequate and well-controlled investigations" on the basis of which it could be concluded that the drug will have the effect it is represented to have under the conditions of the use proposed in labeling
- FDA's regulations (21 C.F.R. § 314.126) describes the essential characteristics of adequate and well-controlled investigations, which include randomized placebo-controlled trails

Advertising

- Under FDA law, “advertisement” refers narrowly to promotional messages that appear in a limited set of traditional media: print media (journals, magazines, newspapers), radio, television, and telephone
- FDA regulations (in language more than 50 year old) define advertisements as follows:

  > “Advertisements . . . include advertisements in published journals, magazines, other periodicals, and newspapers, and advertisements broadcast through media such as radio, television, and telephone communication systems.”

  21 C.F.R. § 202.1(*l*)(1)

Label and Labeling

- "**Label**" – "display of written, printed, or graphic information on the immediate container." FDCA § 201(k)
- "**Labeling**" – the label and "other written, printed, or graphic matter … accompanying" the drug. FDCA § 201(m)

Kordel v. United States (1948):

"One article or thing is accompanied by another when it supplements or explains it, in the manner that a committee report of the Congress accompanies a bill. No physical attachment one to the other is necessary. It is the textual relationship that is significant."

Labeling: Approved versus Promotional

- **Approved labeling** – prescribing information ("PI"), FDA-approved patient labeling (Medication Guides, Instructions for Use, Patient Information, Patient Package Inserts), carton and container labeling
- **Promotional labeling** – everything else
  - Labeling in FDA's regulations includes:

    "Brochures, booklets, mailing pieces, detailing pieces, file cards, bulletins, calendars, price lists, catalogs, house organs, letters, motion picture films, film strips, lantern slides, sound recordings, exhibits, literature, and reprints and similar pieces of printed, audio, or visual matter descriptive of a drug and references published (for example, the ''Physicians Desk Reference'') for use by medical practitioners ...."

    21 C.F.R. § 202.1(*l*)(2)
  - Labeling also includes new media: search engines (i.e., Google "ads"), websites, social media, and email marketing

Misbranding Under FDCA § 502

A drug or device shall be deemed to be misbranded—

(a)(1) If its ***labeling is false or misleading in any particular****.*

…

(f) Unless its labeling bears (1) ***adequate directions for use*** *…*

…

(n) . . . unless th *all*
advertisements *to be issued by*
the manufacture ***statement*** *of . . .*
other informatio *tions, and*
effectiveness as

The "squeeze play":

- "Adequate directions" required for all intended uses
- Promotion establishes new intended use (including advertising, oral statements)
- Can only provide adequate directions through PI
- PI doesn't cover new intended use, 502(f) violation
- Also could be an unapproved new drug violation

Misbranding

- Misbrand depends on not only "**representations made or suggested by statement, word, design, device, or any combination thereof**," but also the extent to which the labeling or advertising "**fails to reveal**" material facts. FDCA § 201(n)

Basic Principles of Drug Promotion

- Consistency with Labeling
- Fair Balance
- Substantiation
- Not Otherwise False or Misleading
- PI Included (for Labeling)
- Brief Summary (for Ads)
- Submission to OPDP/APLB*

*Prior submission for accelerated approval products and certain DTC TV ads

Common Promotional Issues

- Omitting or minimization of risk
- Overstating the drug's benefits (broadening of indication)
- Failing to present a "fair balance" of risk and benefit information
- Omitting material facts about the drug
- Making claims that are not appropriately supported (substantiated)
- Misrepresenting data from studies
- Making misleading drug comparisons (Unsubstantiated superiority/comparative claims)
- Misbranding an investigational drug (pre-approval promotion)
- Quality-of-life Claims
- Off-label promotion

Poll #1

Advertisements on a webpage about a prescription drug require a true statement in brief summary relating to side effects, contraindications, and effectiveness of the drug.

- *True*

or

- *False*

Types of Claims

On, Off, and Consistent With

- **On-Label**: Information expressly contained in FDA-required labeling
- **Off-Label**: Information that could trigger the need for supplemental information
- **Consistent-with-Labeling**: All other information about a medical product

The Off-Label Dilemma

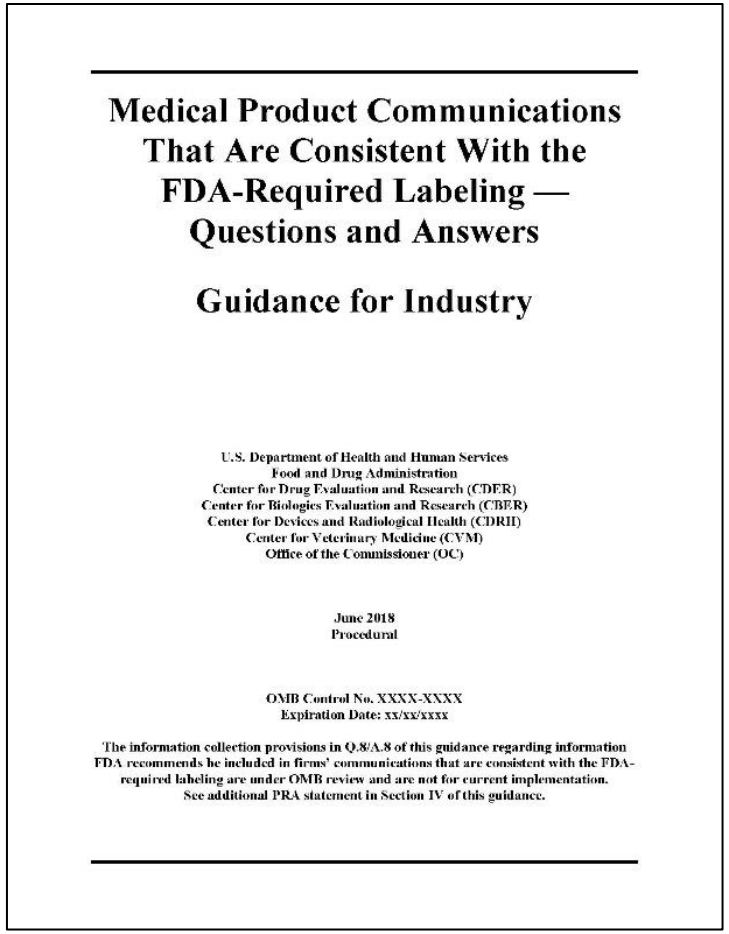
- Off-label use may be important for patient care
  - Doctors may prescribe approved drugs for unapproved uses
  - Approved labeling may lag medical science
  - Off label use may be accepted medical practice, supported by literature, and reimbursable

BUT

- Companies may not promote for these uses

Three-Factor Test for Consistency with Labeling

1. **To be consistent with FDA-approved labeling (CFL), the answer to all the following questions must be yes:**
   - Same indication?
   - Inside the approved patient population?
   - No conflict with directions for use?
   - No conflict with dosage, use regimen, route of administration, or strength?
2. **It must not increase the potential for harm**
3. **The directions for use in FDA-required labeling must allow the product to be used safely and effectively**



Medical Product Communications That Are Consistent With the FDA-Required Labeling — Questions and Answers

Guidance for Industry

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)
Center for Veterinary Medicine (CVM)
Office of the Commissioner (OC)

June 2018
Procedural

OMB Control No. XXXX-XXXX
Expiration Date: xx/xx/xxxx

The information collection provisions in Q.8/A.8 of this guidance regarding information FDA recommends be included in firms' communications that are consistent with the FDA-required labeling are under OMB review and are not for current implementation. See additional PRA statement in Section IV of this guidance.

Scientifically Appropriate and Statistically Sound

- **SASS:**
  - "To be truthful and nonmisleading, representations or suggestions made by firms about their products need to be grounded in fact and science and presented with appropriate context. Any data, studies, or analyses relied on should be scientifically appropriate and statistically sound to support the representations or suggestions made in a CFL promotional communication."
- **Substantial Evidence Not Required**
  - "FDA would not consider representations or suggestions in a CFL promotional communication to be false or misleading based only on the lack of evidence sufficient to satisfy the applicable approval/clearance standard. For example, evidence other than that which meets the new drug approval standard of 'substantial evidence' of effectiveness could be used to support certain representations or suggestions about a prescription drug in a CFL promotional communication."

Context is Critical: Speaker and Forum

- Disease awareness
- Scientific exchange (e.g., medical meetings)
- Press releases and other investor communications
- Websites (branded und unbranded)
- Social media
- Patients vs. Physicians vs Payors

"Scientific Exchange" v. "Promotion"

Scientific Exchange

- Unsolicited med info responses
- Support for independent scientific/educational programs
- Good reprint dissemination
- Bona fide publications/ presentations in scientific fora
- Bona fide research and advisor discussions
- Press releases?
- Other?

Promotion

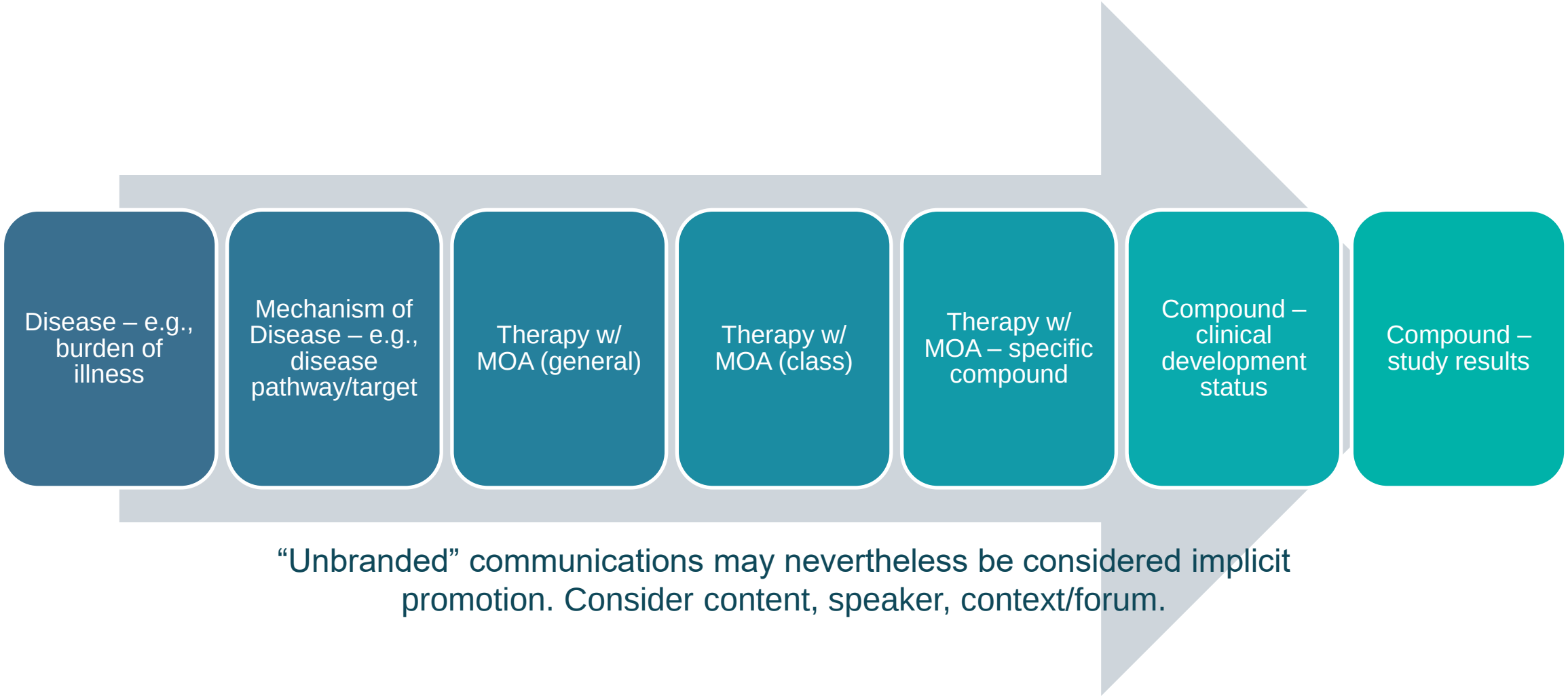
- Advertising
- Promotional "labeling"
- Other activities that show "intended use" (e.g., detailing)

Corporate/IR communications?

Help Seeking & Disease Awareness Communications

- Not FDA-regulated, unless cross the line
- Implicit product pieces?
  - Linkages with product promotion
  - Discussion of treatment/treatment benefits goes too far
- Consider any undue focus on a particular aspect of disease that is inconsistent with the product's label

“Unbranded” Communications



“Unbranded” communications may nevertheless be considered implicit promotion. Consider content, speaker, context/forum.

Unsolicited Requests

- What is an unsolicited request?
  - Genuinely unsolicited; no prompting
  - No broad, open-ended requests
- Responses
  - Tailored to question
  - Balanced, non-promotional response
- Who can respond?
  - HQ Medical Information v. MSLs
  - Medical Info/MSLs v. Sales reps
- FDA guidance: public vs private requests

Reminder Ads and Reminder Labeling

- Focus on name with no information on uses
  - Can include name, ingredients, dosage form, package quantity, price
  - No suggestion of use, including graphics/logos
- May not be used for black box products
  - *Except* price information

Healthcare Economic Information to Payors on Approved Products

Healthcare economic information (HCEI) …

... to payors, formulary committees, and similar entities …

… related to an approved indication …

supported by competent and reliable scientific evidence (CARSE)

Competent and reliable scientific evidence (CARSE)

- **Competent and reliable scientific evidence**
  - “Competent and reliable scientific evidence”
  - Standard for healthcare economic information under section 502(a) of the FDCA
  - FTC standard for health and safety claims in advertising
  - FTC description: “tests, analyses, research, studies, or other evidence based on the expertise of professionals in the relevant area, that has been conducted and evaluated in an objective manner by persons qualified to do so, using procedures generally accepted in the profession to yield accurate and reliable results”
  - Formerly, FDA said this was used for claims that do not suggest a treatment benefit (e.g., convenience)
  - Two randomized controlled clinical trials not required

Poll #2

While healthcare economic information may be supported by competent and reliable scientific evidence, claims about the effectiveness of a prescription drug must be supported by substantial evidence.

- *True*

or

- *False*

Traditional and Other Forums

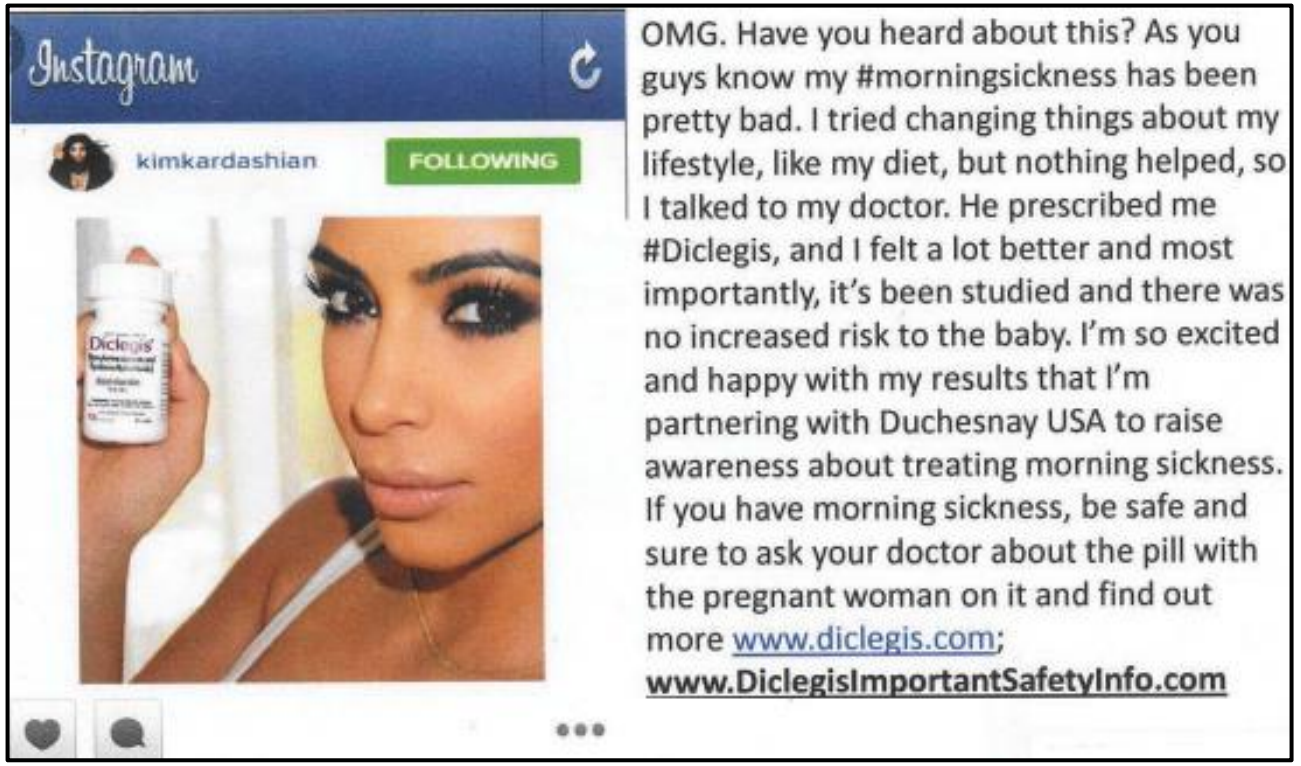
DTC Broadcast Advertisements

- Print advertisements must contain information in "brief summary"
- Advertisements broadcast through television and radio must include:
  - The "major statement," which discusses the major risks of the product
  - Adequate provision: brief summary or adequate provision for dissemination of the PI (toll-free number, print advertisement referenced in broadcast advertisement, webpage, healthcare providers)

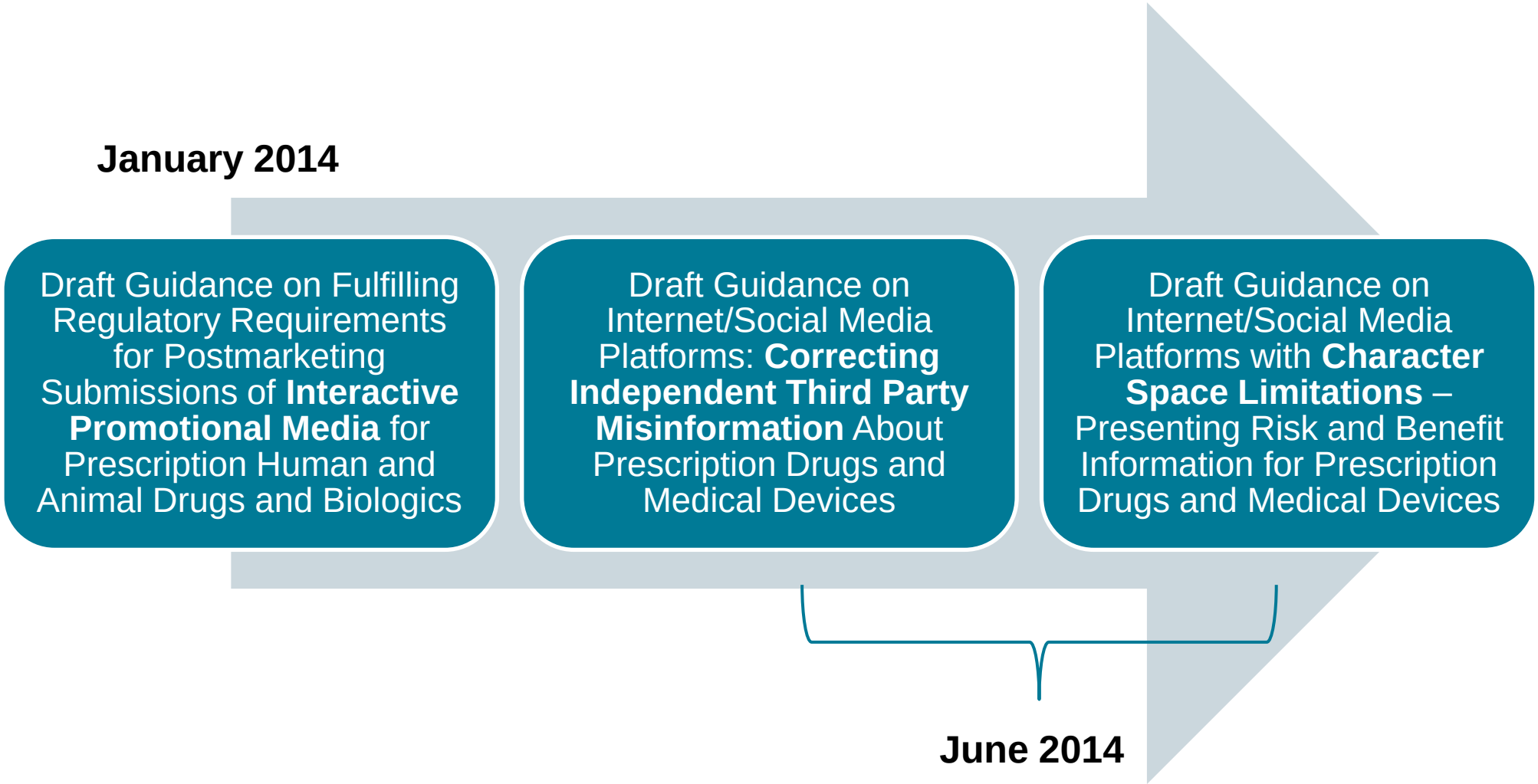
- FDA can require the submission of any television advertisement not later than 45 days before dissemination of the television advertisement. In its draft guidance, FDA has identified six categories for pre-dissemination review.

Social Media -- 2015 Warning Letter to Duchesnay, Inc. for Instagram Post

- "The social media post is false or misleading in that it **presents efficacy claims** for DICLEGIS, but **fails to communicate any risk information**."
- "Thus, the social media posts **misbrands** DICLEGIS **. . .** and **makes its distribution violative**."



FDA's Social Media Guidance



Types of Corporate Communications

Corporate websites

Corporate social media accounts

Investor communications

Press releases

Media interviews and associated messaging documents

Pitch materials

Press Releases

- 21 C.F.R. § 312.7
  - Recognizes “dissemination of scientific findings in scientific or lay media”
  - BUT, can cross the line
- FDA may consider a press release to be promotional labeling if it “makes any representation or suggestion related to the use of an identifiable drug product” and “is issued by or on behalf” of the sponsor
- Key considerations
  - Legitimate news
  - Objective, factual, scientific, and data-driven
  - No safety or efficacy claims
  - Non-promotional in tone
  - No cherry-picking
- Consider subsequent use

Preapproval Communications

Confidentiality

An investigational new drug application is Confidential:

> "**The existence** of an investigational new drug application will not be disclosed by FDA **unless it has previously been publicly disclosed or acknowledged**."

21 C.F.R. 312.130(a)

Note: Similar confidentiality for NDAs and BLAs prior to approval. 21 C.F.R. 314.430(b); 21 C.F.R. 601.50(b)

Bar on Pre-Approval Promotion

21 C.F.R. § 312.7 Promotion of investigational drugs.

(a) Promotion of an investigational new drug. A sponsor or investigator, or any person acting on behalf of a sponsor or investigator, **shall not represent in a promotional context that an investigational new drug is safe or effective** for the purposes for which it is under investigation or otherwise promote the drug. **This provision is not intended to restrict the full exchange of scientific information concerning the drug, including dissemination of scientific findings in scientific or lay media**. Rather, its intent is to restrict promotional claims of safety or effectiveness of the drug for a use for which it is under investigation and to preclude commercialization of the drug before it is approved for commercial distribution.

Guardrails for Pre-Approval Communications

- Must be non-promotional/non-commercial context (except permitted pre-approval to payors)
- No safety/efficacy claims are permitted
  - Describe the data, not the safety/efficacy conclusions you believe should be drawn
- All information presented must be truthful, non-misleading, and non-promotional in tone
  - Include relevant risk/safety information
- Disclaimers indicating that information concerns unapproved or investigational products and/or uses should be prominent
- Content should be segregated from branded or promotional messaging, e.g.:
  - Dedicated research and development section of the corporate (not product) website
  - Franchise website (e.g., Company Oncology, Company Neuroscience)
  - Medical booths at conferences (w/o commercial personnel)

Submissions

Form FDA 2253

- Promotional Submission Requirements
  - Postmarketing submission of promotional materials using Form FDA 2253 at the time of initial dissemination
- Special Pre-Submission Requirements for Accelerated Approval Products
  - During preapproval review, all promotional materials, intended for dissemination within 120 days following marketing approval must be submitted
  - Other materials must be submitted at least 30 days before dissemination

Advisory Comments

- Requesting Advisory Comments
  - Companies can submit promotional materials (including CFL communications) for advisory comments
  - If requesting advisory comments, OPDP often recommends providing annotated references to support the claims and presentations in the promotional material

Thank You

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