Regulation of Drug Marketing: Advertising & Promotion Basics

Heidi F. Gertner
Partner, Hogan Lovells

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Hogan Lovells

FDLI

Agenda

- FDA Basics
- Key Requirements for Promotional Materials
- Common Pitfalls/Enforcement
- Consistent with Guidance
- Safe Harbors
  - Scientific Exchange
  - Speaking with Payors
  - Disease Awareness

FDA Basics

Key Laws: The Federal Food, Drug & Cosmetic Act

- Through the statute, implementing regulations, and guidance, FDA:
  - **Prohibits the promotion of unapproved drugs and devices**
  - **Prohibits the promotion of approved drugs/devices for unapproved uses**
    - Products are misbranded if they do not having adequate directions for all "intended uses"
    - Products violate the "new drug" provision
  - Provides "safe harbors" for certain communications about unapproved uses and unapproved drugs and devices – *e.g.,*
    - Non-promotional "scientific exchange"
    - Good Reprint Practices
    - Responses to "unsolicited requests" for information about unapproved uses

Key Laws: The Federal Food, Drug & Cosmetic Act

- Includes civil and criminal **penalties** for violating the FDCA or causing a violation
  - Enforcement letters
  - Seizure of product
  - Injunction against further violations
  - Criminal penalties
    - Misdemeanor does not require intent, can carry a 1-year sentence, $200,000 fine
    - Violation committed with intent to defraud or mislead, or second violation after a conviction is a felony, with 3-year sentence, $500,000 fine

New Drug Provision

Section 505(a):

"No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) is effective with respect to such drug."

Misbranding Provision

- *Section 502(a)*: A "drug or device shall be deemed to be misbranded . . . [i]f its labeling is false or misleading **in any particular**." (emphasis added). For instance:
  - The **labeling** fails to reveal material facts
  - The **labeling** omits or minimizes risk information or overstates the efficacy of the drug
  - The **labeling** lacks adequate directions for all "intended uses"
  - Claims are not adequately substantiated

Key Definitions: Labeling

- "**Labeling**"
  - "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." 21 USC 321(m)
  - has a **broad** meaning, interpreted to mean items with a "textual relationship to the drug" – brochures and booklets, mailed materials including letters to patients, videotapes, circulars, press releases, slides, e-mail, etc.
    - **No physical attachment** between materials/article is necessary
  - May not include, for instance, certain corporate communications, business correspondence, materials provided to legitimate consultants as part of legitimate services being rendered
  - 2 types: (1) FDA-required labeling and (2) promotional labeling, which is any labeling, other than FDA-required labeling, that is devised for promotion

Key Definitions: Label

- "**Label**"
  - "a display of written, printed, or graphic matter upon the **immediate container** of any article; and a requirement made by or under authority of this chapter that any word, statement, or other information appear on the label shall not be considered to be complied with unless such word, statement, or other information also appears on the outside container or wrapper, if any there be, of the retail package of such article, or is easily legible through the outside container or wrapper." 21 USC 321(k) (emphasis added).

Key Definitions: Advertisements

- "**Advertisements**"
  - FDCA does not define this, but regulations provide examples
  - Advertisements generally appear in
    - Print periodicals, such as journals, magazines, and newspapers
    - Broadcast media, such as television and radio, as well as through telephone systems
  - Promotional labeling differs from advertising in the way it is **distributed**.
    - Ads are usually broadcast on TV or radio, or are published in newspapers or magazines.
    - Promotional labeling includes additional types of materials and ways to get them to the consumer

What is “Promotional?”

Promotional Activity:

- Product details
- Sales aids
- Slides decks used proactively
- Speaker programs
- Commercial display booth
- Advertisements
- Most everything else not listed as non-promotional

Non-Promotional Activity:

- Scientific exchange
- Responses to unsolicited requests
- Dissemination of certain off-label reprints
- Legitimate consultant meetings
- Research
- Scientific publications
- Sponsorship of independent CMEs
- Disease awareness

Indicia of Promotional/Non-promotional Activity

Promotional Activity:

- External audience
- Makes a product claim
- Communication that makes conclusions about the safety/efficacy of a drug product
- Company controls or influences content or pays a third party to do so

Non-Promotional Activity:

- Internal purposes
- No product claim; non-promotional tone
- No claims regarding the product's safety or effectiveness
- Either no company control over content or handled by Medical

Key Requirements for Promotional Materials

Key Requirements for Promotional Materials

- Required Information/Required Accompanying Information
- Disclosing Risk Information to Consumers
- Fair Balance
- Truthful and Non-Misleading
- Consistent with Approved Label
- Adequate Substantiation

Required Information

- Promotional pieces about a drug must include (21 USC 352(n))
  - the **established name** at least ½ as large as the trade name
  - a **quantitative ingredient list** & at least **one dosage form**

  (202.1(d)(2))
  - "**brief summary** relating to side effects, contraindications, and

  effectiveness" though exception for reminder ads
    - This includes "side effects, warnings, precautions, and contraindications and include any such information under such headings as cautions, special considerations, important notes, etc.) and effectiveness (21 CFR 202.1(e)(1))

- For published DTC ads: "You are encouraged to report negative side effects of prescription drugs to the **FDA**. Visit www.fda.gov/medwatch%20or%20call%201-800-FDA-1088" (21 USC 352(n)(3))
- Must submit to FDA on **Form 2253**

Required Accompanying Information

- **Full indication** if mention any benefit or any claim (*i.e.,* statement about the product)
- **PI** (to fulfill "adequate directions for use" requirement) for HCPs
  - for consumers, industry includes PI, but FDA recommends against it (to be discussed)
  - Drug labeling generally must bear "adequate directions for use" (21 USC 352(f)(1)), but Rx drugs are exempt from this requirement if certain conditions are met

Required Accompanying Information

- 21 CFR 201.100(d) requires the labeling to contain:
  - "**Adequate information for such use**, including indications, effects, dosages, routes, methods, and frequency and duration of administration and any relevant warnings, hazards, contraindications, side effects, and precautions, under which practitioners licensed by law to administer the drug can use the drug safely and for the purposes for which it is intended, including all conditions for which it is advertised or represented; and if . . . the parts of the labeling providing such information are the **same in language and emphasis as labeling approved** or permitted . . and any other parts of the labeling are consistent with and not contrary to such approved or permitted labeling; and
  - The information required, and in the format specified, by §§201.56, 201.57, and 201.80 (labeling requirements)"
- Requirement is met in broadcast ads by providing sources for finding PI

Disclosing Risk Information to Consumers

- Traditionally:
  - To fulfill the **brief summary requirement**—consumer-directed print ads for Rx drugs usually include the complete risk-related sections of the PI
  - To fulfill the **adequate directions for use requirement**—promotional pieces generally include the full PI
- FDA's draft guidance (*Brief Summary and Adequate Directions for Use: Disclosing Risk Information in Consumer-Directed Print Advertisements and Promotional Labeling for Prescription Drugs*) (Aug. 2015) recommends alternative approaches companies can use to fulfill the requirements

Disclosing Risk Information to Consumers

- FDA recommends **against**:
  - Fulfilling the brief summary requirement by **presenting risk related sections of the PI often verbatim and in small font**
  - **Providing the full PI** to satisfy the adequate directions for use requirement for consumer directed print promotional labeling pieces for Rx drugs

- Instead, FDA recommends using the **“consumer brief summary”**

Disclosing Risk Information to Consumers

- Language and Readability
  - Use **consumer-friendly** language
  - Write in language designed for understanding by a broad audience with **various levels of literacy skills**
  - **Avoid** technical language, scientific terms, medical jargon
  - Use **conversational** tone *e.g.,* “do not use if you have” instead of “contraindications”
  - Present in a **readable** format
    - Use headlines and subheadings
    - Focus on layout, font size, type size (use double spacing, indentations, maximize white space, text boxes)

Disclosing Risk Information to Consumers

- Content
  - The consumer brief summary should provide clinically significant information on the most serious and most common risks associated with the product – and omit less pertinent information (look to FDA-approved patient labeling and Med Guides)
  - Rely on criteria used for selecting risk information for Highlights section of PI to determine what risk info to include—but with more detail than Highlights
  - Use order from Highlights section (Boxed Warning, then Contraindications, then Warnings and Precautions….)

Disclosing Risk Information to Consumers

- Content continued…
  - Include in brief summary:
    - Boxed Warning
    - All Contraindications
    - Certain Warnings and Precautions Information:
      - Most clinically significant information from the W and P section of the PI
      - Information that would affect a decision to take the drug
      - Monitoring or lab tests needed
      - Special precautions
      - Measures that can be taken to mitigate harm

Disclosing Risk Information to Consumers

- Content continued…
  - Include in brief summary:
    - Most frequently occurring **adverse reactions** (for each indication if more than one) in order listed in PI
    - Also include **serious adverse reactions and those that lead to discontinuation** of drug or adjustment to dose
    - Other **material information** – severity of risks, early warning signs of risks, monitoring during treatment, etc
    - The **indication** for use
    - Clinically significant **drug interactions**
    - **Information relevant to discuss with doctors**
    - **Special population** information
    - **Duration of use**

Disclosing Risk Information to Consumers

- **No need to include** in the brief summary (most of the time):
  - Dosage and administration information
  - How the drug is supplied
  - The clinical pharmacology
  - Specific directions for use
  - How long drug takes to work

Disclosing Risk Information to Consumers

- FDA also recommends including statements:
  - Reminding consumers that the information is **not comprehensive**
  - Suggesting that consumers **talk to their HCP**
  - Containing a toll free number or website address where FDA **approved labeling can be obtained**
- Reminder:
  - If the PI is revised, review and **revise the brief summary accordingly**

Fair Balance

- Must include a **"fair balance" about risks as compared with benefit** information (202.1(e)(5)(ii))
  - For instance, content and presentation of most important risks must be reasonably similar to content and presentation of benefits (e.g., prominence, and readability)
- Reminder ads/labeling are exempt (202.1(e)(2)(i))
- Companies use **ISI** to help fulfill fair balance requirements
  - Consumer vs HCP
- **Boxed warnings** should receive emphasis; consider placement

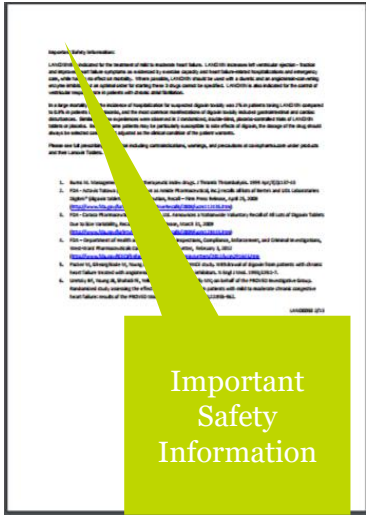
Vyvanse™ (lisdexamfetamine dimesylate) **C- II Rx Only**

AMPHETAMINES HAVE A HIGH POTENTIAL FOR ABUSE. ADMINISTRATION OF AMPHETAMINES FOR PROLONGED PERIODS OF TIME MAY LEAD TO DRUG DEPENDENCE. PARTICULAR ATTENTION SHOULD BE PAID TO THE POSSIBILITY OF SUBJECTS OBTAINING AMPHETAMINES FOR NON-THERAPEUTIC USE OR DISTRIBUTION TO OTHERS AND THE DRUGS SHOULD BE PRESCRIBED OR DISPENSED SPARINGLY.

MISUSE OF AMPHETAMINE MAY CAUSE SUDDEN DEATH AND SERIOUS CARDIOVASCULAR ADVERSE EVENTS.

Fair Balance

- **Presentation pitfalls**
  - backside of poster
  - paragraph format with no headings
  - small font, bottom of the piece
  - not part of the body of the piece
  - not clear where to go to locate
  - hyperlinking to risk info (one-click myth)

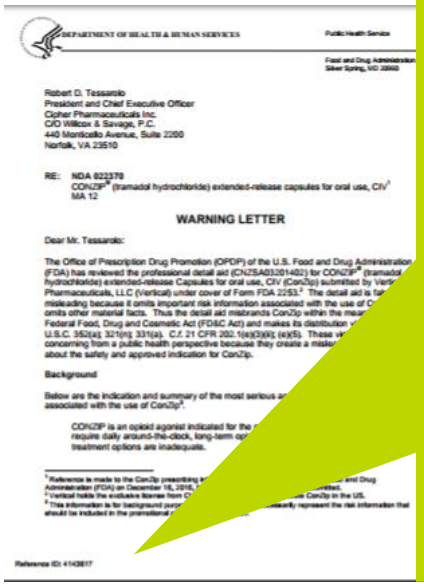


FDA Untitled Letter to Covis Pharmaceuticals (Dec. 9, 2013)

" The letter prominently presents efficacy claims in the body of the letter . . . In contrast, the limited risk information that is included is presented on the back side of the letter after the signature block, in significantly smaller type print, and with a reference to actively search out a separate source for the complete risk information."

Fair Balance

Warning Letter to Cipher Pharmaceuticals (Aug. 24, 2017) re CONZIP (tramadol hydrochloride) ER Capsules


DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Robert D. Tessarolo
President and Chief Executive Officer
Cipher Pharmaceuticals Inc.
C/O Wilcox & Savage, P.C.
440 Monticello Avenue, Suite 2200
Norfolk, VA 23510

RE: NDA 022378
CONZIP® (tramadol hydrochloride) extended-release capsules for oral use, CIV
MA 12

WARNING LETTER

Dear Mr. Tessarolo:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed the professional detail aid (CNZSAID3014421) for CONZIP® (tramadol hydrochloride) extended-release Capsules for oral use, CIV (ConZip) submitted by Vertical Pharmaceuticals, LLC (Vertical) under cover of Form FDA 2253.[1] The detail aid is false or misleading because it omits important risk information associated with the use of ConZip and omits other material facts. Thus the detail aid misbrands ConZip within the meaning of the Federal Food, Drug and Cosmetic Act (FD&C Act) and makes its distribution violative of 21 U.S.C. 352(a); 321(n); 331(a). C.F. 21 CFR 202.1(e)(3)(i); (e)(5). These violations are concerning from a public health perspective because they create a misleading impression about the safety and approved indication for ConZip.

Background

Below are the indication and summary of the most serious risks associated with the use of ConZip[2].

CONZIP is an opioid agonist indicated for the management of pain severe enough to require daily around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

[1] Reference is made to the ConZip prescribing information submitted to the Food and Drug Administration (FDA) on December 16, 2016.

[2] Vertical holds the exclusive license from Cipher to market ConZip in the US.

[3] This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional piece.

Reference ID: 4143817

"The detail aid makes representations and/or suggestions about the efficacy of ConZip such as the following: . . . "All Day Pain Relief" . . . . However, [it] fails to communicate **any** risk information about the product. . . [a]nd creates a misleading impression about the drug's safety"

Fair Balance

- **Digital Space**
  - **Rules of Thumb**—from industry practices and advisory comments
    - Safety information should take up **at least ¼ of screen**
    - "Above the fold" for websites
    - If **Black Box Warning** drug:
      - Make box visible on screen (shouldn't need to scroll down to see it)
      - Consider using static box or including the black box at the top as a header
    - Use an **expandable** box for the brief summary (not running text at bottom of screen)
    - Pay attention to **colors and shading** from dark to light (ombré effect)
    - Pay attention to **speed/pace** of scrolling information
    - On consumer sites, be sure to use **patient friendly language**

Fair Balance

- **Social Media**
  - FDA's Draft Guidance "*Internet/Social Media Platforms with Character Space Limitations – Presenting Risk and Benefit Information for Prescription Drugs and Medical Devices*" (June 2014) **acknowledges the challenges in character-space limited platforms**
    - FDA cautions against use of these platforms for certain products, "particularly those with complex indications or extensive serious risks"
    - If product benefit claim is made within a character-space limited communication, the company must also:
      - **incorporate risk info in that same character-space limited communication** (*e.g.*, each individual message or tweet)

Fair Balance

- **Social Media**
  - Content of risk info in the **character-space limited communication must include, at least, the most serious risks** for a drug that would mean all risk concepts from the boxed warning, all risks known to be fatal or life-threatening, and all contraindications
  - If the drug does not have a boxed warning, the most significant warnings or precautions about the product
  - provide a mechanism to allow direct access to a more complete discussion of risks (e.g., a direct hyperlink to a destination of page **exclusively** discussing risk info, so not a home page that includes benefit info); URL shortening is okay
  - Risk info must be as prominent as benefit info

Truthful and Non-Misleading

- Determination includes, **representations made or suggested, or failure to reveal facts** in light of representations made by materials
- Disclose **material facts** and provide necessary **context**
- **Avoid overstatement** of product efficacy and safety
- Examples of misleading presentation include:
  - Contains favorable information or conclusions from a single study that is **inadequate in design, scope or conduct** to furnish significant support for such information or conclusions;
  - Uses statistical analyses and techniques on a **retrospective** basis to discover and cite findings **not soundly supported by the study**, or to suggest scientific validity and rigor for data from studies the design or protocol of which are **not amenable to formal statistical evaluations**. 21 CFR 202.1(e)(7)

Truthful and Non-Misleading

Untitled Letter to Orexigen Therapeutics (May 18, 2017) re CONTRAVE (naltrexone HCl and bupropion HCl) ER Tablets

Orexigen Therapeutics, Inc. (Contrave) Untitled Letter 5/18/2017

FDA U.S. FOOD & DRUG ADMINISTRATION

Stacy Hennings
Sr. Director, Regulatory Affairs Advertising & Promotions
Orexigen Therapeutics, Inc.
3344 North Torrey Pines Ct., Ste. 200
La Jolla, CA 92037

RE: NDA 200063
CONTRAVE (naltrexone HCl and bupropion HCl) Extended-Release Tablets
MA 301

Dear Ms. Hennings:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed

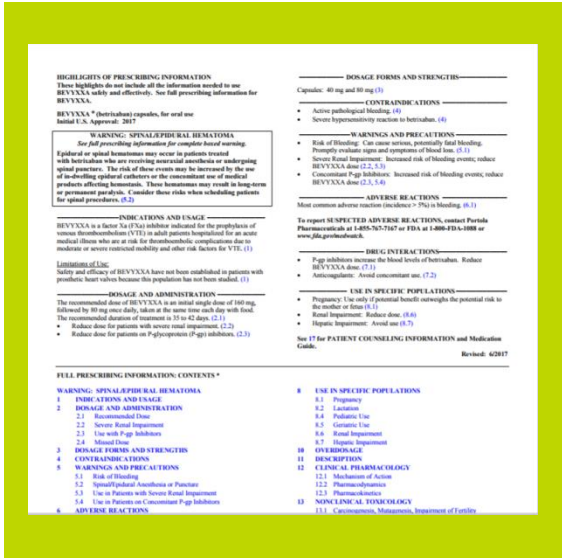
"The TV ad is also **misleading** because it communicates important risk information in the visual portion of the TV ad only, *i.e.*, as SUPERs, and presents unrelated risk information in competing audio messages"

SUPER: NAUSEA, CONSTIPATION, HEADACHE AND VOMITING OCCURRED IN >10% OF PATIENTS

Do not take with opioids.

Consistent with the Approved Label

- The communication must be consistent with FDA-required labeling, otherwise FDA could view it as a new intended use
  - More on this in a moment



HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BEVYXXA safely and effectively. See full prescribing information for BEVYXXA.

BEVYXXA ® (betrixaban) capsules, for oral use
Initial U.S. Approval: 2017

WARNING: SPINAL/EPIDURAL HEMATOMA
See full prescribing information for complete boxed warning.
Epidural or spinal hematomas may occur in patients treated with betrixaban who are receiving neuraxial anesthesia or undergoing spinal puncture. The risk of these events may be increased by the use of in-dwelling epidural catheters or the concomitant use of medical products affecting hemostasis. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. (5.2)

INDICATIONS AND USAGE
BEVYXXA is a factor Xa (FXa) inhibitor indicated for the prophylaxis of venous thromboembolism (VTE) in adult patients hospitalized for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE. (1)

Limitations of Use:
Safety and efficacy of BEVYXXA have not been established in patients with prosthetic heart valves because this population has not been studied. (1)

DOSAGE AND ADMINISTRATION
The recommended dose of BEVYXXA is an initial single dose of 160 mg, followed by 80 mg once daily, taken at the same time each day with food. The recommended duration of treatment is 35 to 42 days. (2.1)
- Reduce dose for patients with severe renal impairment. (2.2)
- Reduce dose for patients on P-glycoprotein (P-gp) inhibitors. (2.3)

DOSAGE FORMS AND STRENGTHS
Capsules: 40 mg and 80 mg (3)

CONTRAINDICATIONS
- Active pathological bleeding. (4)
- Severe hypersensitivity reaction to betrixaban. (4)

WARNINGS AND PRECAUTIONS
- Risk of Bleeding: Can cause serious, potentially fatal bleeding. Promptly evaluate signs and symptoms of blood loss. (5.1)
- Severe Renal Impairment: Increased risk of bleeding events; reduce BEVYXXA dose (2.2, 5.3)
- Concomitant P-gp Inhibitors: Increased risk of bleeding events; reduce BEVYXXA dose (2.3, 5.4)

ADVERSE REACTIONS
Most common adverse reaction (incidence > 5%) is bleeding. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Portola Pharmaceuticals at 1-855-767-7167 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS
- P-gp inhibitors increase the blood levels of betrixaban. Reduce BEVYXXA dose. (7.1)
- Anticoagulants: Avoid concomitant use. (7.2)

USE IN SPECIFIC POPULATIONS
- Pregnancy: Use only if potential benefit outweighs the potential risk to the mother or fetus (8.1)
- Renal Impairment: Reduce dose. (8.6)
- Hepatic Impairment: Avoid use (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 6/2017

FULL PRESCRIBING INFORMATION: CONTENTS *

Adequate Substantiation

- Substantiation requirement varies based on the type of claim, e.g.,
  - Therapeutic claims
  - Comparative claims
  - Disease awareness claims
  - HCEI claims
- Therapeutic and comparative claims require "substantial evidence," because the regulations state: "An ad/promotion is otherwise misleading if, *e.g.*, it
  - Contains a representation or suggestion, not approved or permitted for use in the labeling, that a drug is better, more effective, useful in a broader range of conditions or patients, or is safer than demonstrated by **substantial evidence** or substantial clinical experience." 21 CFR 202.1(e)(6)(i)

Adequate Substantiation

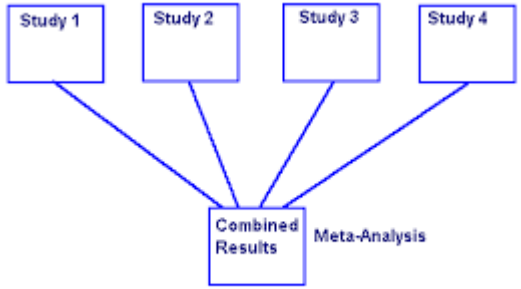
Substantial Evidence

- FDA is required to approve a drug when its safety and effectiveness have been established by "substantial evidence."
  - Section 505(d) of the Act describes substantial evidence consisting 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
- Generally, at least **two** adequate and well-controlled studies, each convincing on its own, to establish effectiveness
  - **21 CFR 314.126** describes the essential characteristics of adequate and well-controlled trials

Adequate Substantiation

Substantial Evidence

- Potential pitfalls:
  - Open-label studies
  - Retrospective subgroup analyses
  - Meta-analyses
  - Reported assessments
  - Patient-reported outcomes (PROs)
  - Clinician-reported outcomes (ClinROs)
  - Observer-reported outcomes (ObsROs)
  - Composite scores



Adequate Substantiation

CARSE (Competent and Reliable Scientific Evidence)

- Disease awareness, non-therapeutic, and HCEI claims must meet CARSE
- CARSE: “tests, analyses, research, studies, or other evidence based upon 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”
- **What It Isn’t:**
  - Anecdotal evidence from customers
  - Newspaper or magazine articles
  - Tests conducted by people who are not qualified

Adequate Substantiation

Scientifically Appropriate and Statistically Sound (SASS)

- For information that MAY BE “consistent with” the labeling
- SASS is a relatively new standard and is not defined by the statute, case law, or regs, but, PhRMA/FDA expect the level of evidence may vary between different types of claims

Common Pitfalls/Enforcement

Common Pitfalls/Considerations for

- **Abbreviation of Indication**
- Absence of Context/

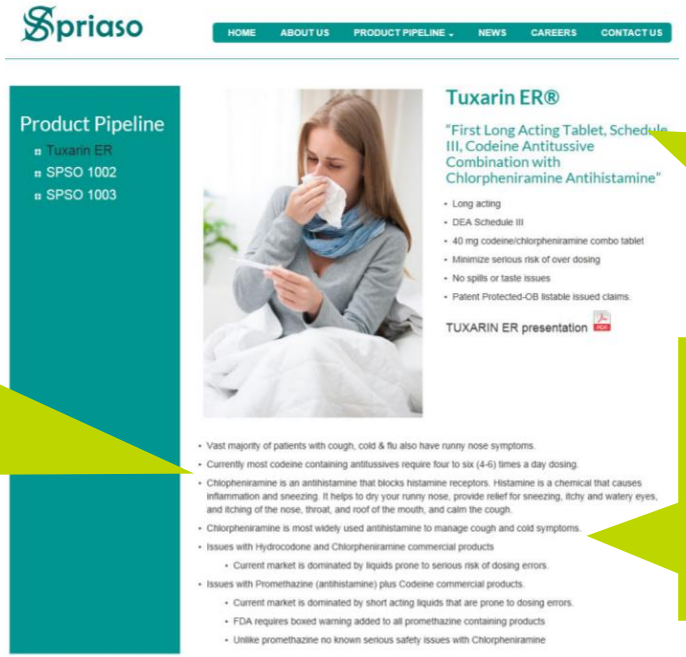
  Selective Presentation of Data
- Pre-Clinical Data
- **Convenience Claims**
- Compliance / Adherence Claims
- **Investigational Drugs**
- **QOL Claims**
- Imagery
- Clinical Practice Guidelines /

  Third-Party Links
- Patient Case Studies
- Duration of Use Claims
- Cost Claims
- Symptom Selling
- MOA Selling
- **Other Comparative Claims**
- Presentation of Risk Information
- Safety Claims

Common Pitfalls/Considerations

- Abbreviation of Indication – Warning Letter to Spriaso, LLC regarding a webpage about Tuxarin ER (codeine phosphate and chlorpheniramine maleate) tablets (Dec. 13, 2016)

Chlorpheniramine . . . helps to dry your runny nose, provide relief for sneezing, itchy and watery eyes, and itching of the nose, throat, and roof of the mouth, and calm the cough



First Long Acting Tablet, Schedule III, Codeine Antitussive Combination with Chlorpheniramine Antihistamine

Chlorpheniramine is most widely used antihistamine to manage cough and cold symptoms

Common Pitfalls/Considerations

- Abbreviation of Indication – Warning Letter to Spriaso, LLC (Dec. 13, 2016)
  - FDA concluded the claims are misleading because they **failed to adequately communicate the full approved indication**, and implied the drug is approved for **all ages**;
  - The agency was particularly concerned given that the drug is a **boxed warning** and has a contraindication in children, which is not disclosed in the piece

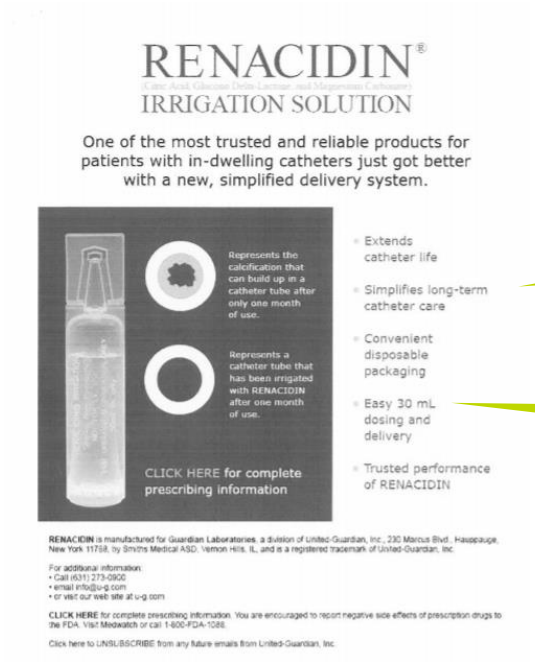
1 INDICATIONS AND USAGE CODEINE PHOSPHATE AND CHLORPHENIRAMINE MALEATE ER TABLETS is indicated for the relief of cough and symptoms associated with upper respiratory allergies or a common cold in adults 18 years of age and older.

Important Limitations of Use

Not indicated for pediatric patients under 18 years of age *[see Use in Special Population (8.4)]*

Common Pitfalls/Considerations

- Convenience Claims – Warning Letter to United-Guardian Inc. regarding a professional email about Renacidin (citric acid, glucono delta-lactone, and magnesium carbonate) Irrigation Solution (Dec. 12, 2016)


RENACIDIN®

IRRIGATION SOLUTION

One of the most trusted and reliable products for patients with in-dwelling catheters just got better with a new, simplified delivery system.

Represents the calcification that can build up in a catheter tube after only one month of use.

Represents a catheter tube that has been irrigated with RENACIDIN after one month of use.

CLICK HERE for complete prescribing information

- Extends catheter life
- Simplifies long-term catheter care
- Convenient disposable packaging
- Easy 30 mL dosing and delivery
- Trusted performance of RENACIDIN

RENACIDIN is manufactured for Guardian Laboratories, a division of United-Guardian, Inc., 230 Marcus Blvd., Hauppauge, New York 11788, by Smiths Medical ASD, Vernon Hills, IL, and is a registered trademark of United-Guardian, Inc.

For additional information:
• Call (631) 273-0900
• email info@u-g.com
• or visit our web site at u-g.com

CLICK HERE for complete prescribing information. You are encouraged to report negative side effects of prescription drugs to the FDA. Visit Medwatch or call 1-800-FDA-1088.

Click here to UNSUBSCRIBE from any future emails from United-Guardian, Inc.

Simplifies long-term catheter care

Easy 30 mL dosing and delivery

Common Pitfalls/Considerations

- Convenience Claims – Warning Letter to United-Guardian Inc. (Dec. 12, 2016)
  - FDA noted that no references were cited to support the claims and the agency was **not aware of supporting evidence**
  - FDA also explained that the email **omitted the following information from the approved physician labeling regarding how the drug should be dosed** and **administered**, which exacerbates the misleading characterization of dosing and delivery in the email:

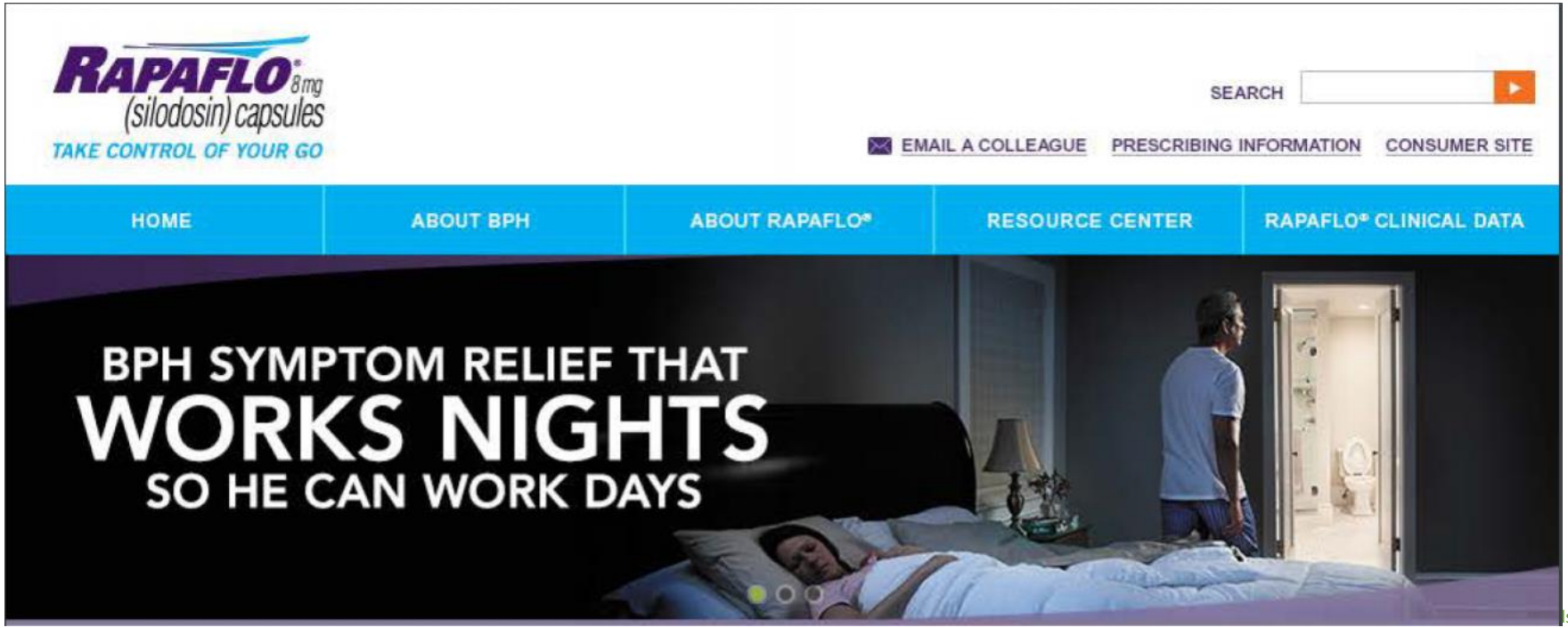
> "Instill 30 mL (one container) of Renacidin into the urethral catheter or cystostomy tube. Clamp the urethral catheter or cystostomy tube for 10 minutes. Remove the clamp and drain the bladder. Repeat the instillation procedure 3 times a day"

Common Pitfalls/Considerations

- Investigational Drug – Untitled Letter to Chiasma Inc. regarding a YouTube video for an investigational new drug octreotide capsules (silodosin) capsules (Dec. 21, 2016)
  - FDA alleged that the video suggests, in a promotional context, that the drug is safe and effective for the purpose for which it is being investigated, or otherwise promotes the drug, *e.g.,*
    - Dr. Melmed: "I think the most important result of the trial was that **the drug is safe** . . . and the physician using the new drug should be assured and be able to reassure his or her patients that in fact **the drug is safe**. Secondly that the drug is efficacious and the **effectiveness of the drug was proven** in the clinical trials in that about 62% of patients who were known to respond to octreotide were shown to achieve the primary endpoint which was a maintenance of normal IGF 1 levels." (emphasis added)
  - The agency acknowledged the statement "Product is an investigational new drug and not available for commercial distribution" in a SUPER at the end of the video, but this did not mitigate the misleading presentation

Common Pitfalls/Considerations

- Quality of Life Claims – Untitled Letter to Actavis Laboratories regarding website for Rapaflo (silodosin) Capsules (May 19, 2015)



Common Pitfalls/Considerations

- Quality of Life Claims – Untitled Letter to Actavis Laboratories (May 19, 2015)
  - FDA determined the presentation was misleading because it implied that in addition to improving benign prostatic hyperplasia (BPH) symptoms (Rapaflo's indication), Rapaflo had been shown to improve quality of sleep and work productivity, but **no references were cited to support this**, and the pivotal studies did not evaluate the impact of the product on sleep quality and work productivity
  - The agency noted that two double-blind, placebo-controlled, multicenter studies had evaluated Rapaflo's effectiveness, and the primary efficacy assessment was the International Prostate Symptom Score (IPSS), which was a composite endpoint that evaluated irritative (frequency, urgency, and nocturia), and obstructive (hesitancy, incomplete emptying, and weak stream symptoms), but the **studies did not measure the impact of the drug on individual symptoms like nocturia**

Common Pitfalls/Considerations

- Other Comparative Claims – Warning Letter to ECR Pharmaceuticals (Valeant) regarding a sales aid for TussiCaps (hydrocodone polistirex and chlorpheniramine polistirex) Extended-release Capsules (Aug. 27, 2015)

Common Pitfalls/Considerations

- Other Comparative Claims – Warning Letter to ECR Pharmaceuticals (Aug. 27, 2015)
  - According to FDA, the claims and presentation were misleading because they suggested that due to their capsule dosage form, patients specifically prefer TussiCaps capsules over oral liquid formulations
  - A study by Harris Interactive is cited to support the patient preference claim for the TussiCaps dosage form (no other references are cited to support the other claims and presentations) and this study was **insufficient to support the claim** because it did not specifically evaluate TussiCaps compared to liquid formulations

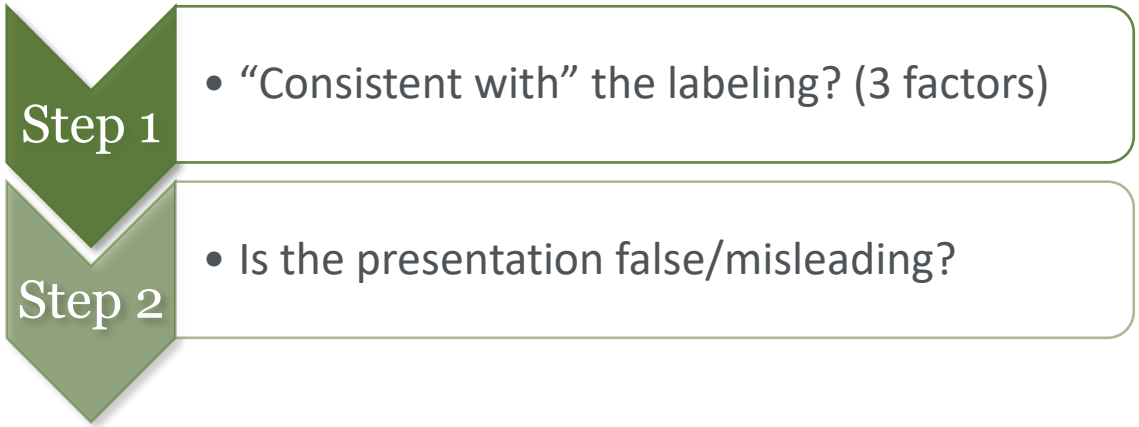
Consistent With Guidance & Safe Harbors

On-Label vs. Off-Label and Consistent With Guidance

- Now:
  - On-label = in the PI
  - Consistent with the label = consistent with the PI
  - Off-label = Not consistent with the PI

Consistent with Approved Label

- Must be consistent with the label, otherwise evidence of a new intended use
- Guidance: Medical Product Communications That Are Consistent With the FDA-Required Labeling – Questions and Answers (June 2018)
  - **Effect of proposed framework:** if FDA reviews a firm's statement and finds it to be adequately supported and consistent with the contents of the required labeling, ***dissemination of that statement will not be considered, by itself, to be evidence of a new intended use***



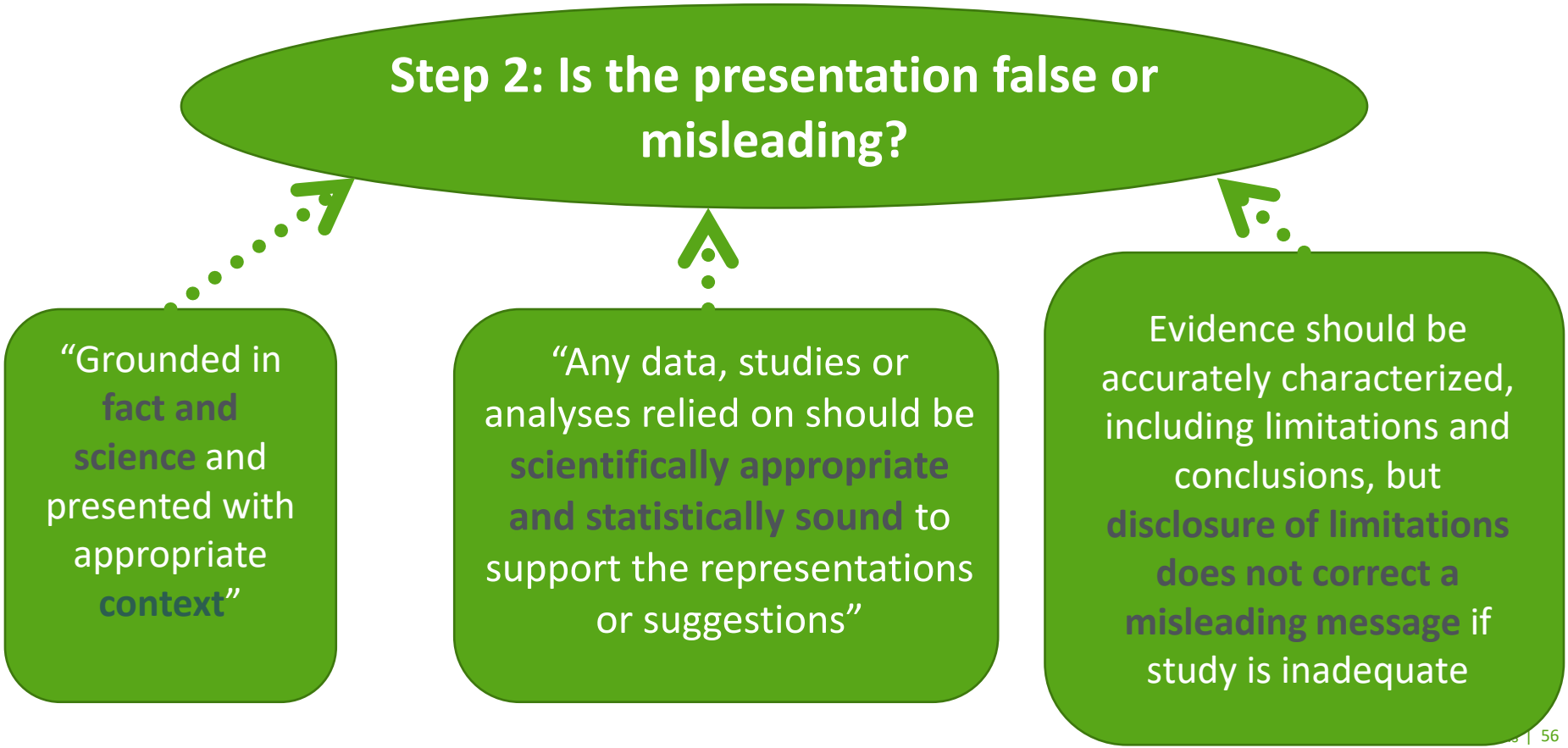
Consistent with Approved Label

- **Factor 1 – Comparison with required labeling.** The following factors must all be true in order for FDA to consider a firm's representation/suggestion to be "consistent" with required labeling:
  - **Indication**. Representation relates only to the indication(s) in the required labeling
  - **Patient Population**. No representations regarding patients outside of approved/cleared patient population in the required labeling
  - **Limitations, Directions for Handling/Use**. No conflict with the use limitations or directions for handling, preparing, and/or using the product in the required labeling
  - **Dosing/Administration**. No conflict with the recommended dosage or use regimen, route of administration, or strength(s) (if applicable) from the required labeling

Consistent with Approved Label

- **Factor 2 – Increased risk of harm**. Whether the firm's representations increase the potential for harm to health as compared to FDA-required labeling information
- **Factor 3 – Directions for use.** Whether following FDA-required labeling directions for use provides for safe and effective product use under the conditions represented/suggested in the company's communication

Consistent with Approved Label



Existing Safe Harbors to Communicate Unapproved Uses

- Scientific Exchange
- Communications with Payors
- Disease Awareness

Scientific Exchange

Scientific Exchange Legal Standard (21 CFR 312.7)

- "A sponsor . . . 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 is under investigation and to preclude commercialization of the drug before it is approved for commercial distribution."

Scientific Exchange: In Brief

- All non-promotional/scientific exchange pre-approval communications must:
  - Disclose that the compound/use is investigational
  - Include appropriate context and disclose all material facts such as failed endpoints and study limitations
  - Be scientifically rigorous
  - Avoid representations that the product is safe or effective
  - Be non-promotional in tone
  - Be balanced (*i.e.*, include a discussion of the potential risks as the possible effectiveness of the compound or use)
  - Provide sufficient context for data presented

Scientific Exchange Regulation – 21 CFR 312.7(a)

- Three sentences:
  - Sponsor shall not represent in a promotional context that an investigational 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*** . . . 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***

Hallmarks

- ***Conveyed*** to the public at medical conferences, through the media, or to investors
- ***By*** those with medical or scientific expertise, e.g. investigators, KOLs, or employees with medical/scientific background
- ***At*** congress, investigators' meeting, exhibit hall
  - FDA does not acknowledge in-office meetings as scientific exchange
- ***Only occasionally*** or when new data are available

Pitfalls

- Content must be *objective, balanced, and scientifically rigorous*
- Non-promotional in tone
- Provide context for data presented, e.g. study design, endpoints
- Be truthful and non-misleading

Scientific Exchange: Details…

- "Scientific exchange" allows publication/discussion of clinical trial results "in the scientific and lay media" that is not promotional (*i.e.*, no conclusions of safety or effectiveness)
  - Concept developed to permit presentation of Phase III data at medical conferences and in corporate statements about material events (e.g. press releases, SEC filings)
- The challenge is assuring that the "context" is not promotional, e.g.
  - The data are rigorous and accurately conveyed without conclusions of safety or effectiveness
  - The setting is appropriately neutral (medical booth vs. commercial booth)
  - The speaker is qualified
  - The frequency of communication is measured

Payor Communications

Communications with Payors

Health Care Economic Information (HCEI)

- Defined in FD&C Act Section 502(a). As amended by 21st Century Cures:
  - **What:** "any analysis (including the clinical data, inputs, clinical or other assumptions, methods, results, and other components underlying or comprising the analysis) that identifies, measures, or describes the economic consequences, which may be based on the separate or aggregated clinical consequences of the represented health outcomes, of the use of a drug."
    - HCEI that "~~directly~~ **relates to**" an approved indication and is based on "competent and reliable scientific evidence" and, if applicable, includes a conspicuous and prominent statement describing material differences between the HCEI and approved labeling"
      - HCEI analyses may also incorporate info not in approved labeling

Communications with Payors

Health Care Economic Information (HCEI)

- **To whom:** Provided to "a payor, formulary committee, or other similar entity with knowledge and expertise in the area of health care economic analysis, carrying out its responsibilities for the selection of drugs for coverage or reimbursement"
- **Effect:** Will not be considered false or misleading, or as evidence of intended use

Communications with Payors

Examples of what DOES "relate to" an approved indication

- HCEI analyses must relate to the disease/condition, or the manifestation or symptoms associated with the disease in the approved patient population
- Separate and distinct analysis from what is "consistent with the label"
- Guidance lists a number of examples of HCEI that could "relate to" an approved indication where it incorporates information not contained in, or varying from in certain respects, approved-labeling information. Examples include analyses based on/of:
  - Long-term use for approved indication over a period different from that described in labeling where indication does not limit use duration
  - Treatment effects in subgroups within approved patient population even where subgroup analyses were not pre-specified
  - Clinical outcome assessments (including patient-reported outcomes) or other health outcome measures not included in the labeling

Communications with Payors

"Relates to" an approved indication

- Examples (Cont'd)
  - Involving different dosage regimens than those approved in the labeling
  - About burden of disease for which product is approved
  - Based on uses of the drug in practice settings that differ from the settings used in the pivotal trials
  - Treatment impact on length of hospital stays
  - Demonstrating an effect on a validated surrogate endpoint that is known to predict clinical benefit (*e.g.,* blood pressure is a validated surrogate endpoint for reduction in certain cardiovascular events)

Communications with Payors

Does NOT "relate[] to" an approved indication

- Examples:
  - Economic analyses of disease course modification for a drug only approved to treat symptoms
  - Analyses based on patient data outside of approved patient population
    - No materiality standard
- Developing HCEI analyses that perfectly match the eligibility criteria of pivotal studies can be difficult and time-consuming
  - No flexibility is explicitly built into FDA's assessment, at least based on the language in the draft guidance

Communications with Payors

Based on "competent and reliable scientific evidence" or CARSE

- Satisfied if developed with generally-accepted scientific standards appropriate for the info being conveyed which yield accurate and reliable results (similar to FTC's standard)
- Standard applies to all aspects of HCEI, including inputs and assumptions related to clinical outcomes
- FDA will consider practices and guidelines developed by authoritative bodies and external expert groups
  - International Society for Pharmacoeconomic and Outcomes Research (ISPOR)
  - Patient-Centered Outcomes Research Institute (PCORI)

Communications with Payors

Location

- Communications should be made:
  - In a location that is appropriate to the recipient's payor role
    - HCPs who also qualify as permissible recipients of the information should not be engaged while in their role as a prescriber
  - In a professional setting that is conducive to discussion
    - *E.g.,* not an entertainment venue

Communications with Payors

How?

- May be proactive
- Information should be physically and temporally separate from other materials that may be permitted to be sent to providers
  - This distinguishes the individual in his or her capacity as a medical practitioner versus an organizational decision-maker
- Materials should have a different "look and feel" from other materials provided
- Companies should provide follow-up info if previously provided info becomes outdated or new information about product becomes available (*e.g.,* review status)

Communications with Payors

HCEI is promotion and is subject to promotion requirements

- FDA clarifies that HCEI dissemination to payors is considered to be promotion, and corresponding requirements apply
- This includes post-marketing submission of promotional materials at the time of first use under 21 CFR 314.81(b)(3)(i)

Communications with Payors

Payor communications regarding investigational drugs

- FDA will not object under its "scientific exchange" regulation if the information is unbiased, factual, accurate, non-misleading, and presented with a clear statement that the drug is under investigation, the stage of product development, and that safety & efficacy have not been established
  - Product info (drug class, device design)
  - Indication info
  - Factual presentations from study results, without conclusory claims
  - Anticipated timeline for possible approval
  - Product pricing info
  - Targeting/marketing strategies
  - Product-related programs or services
- Companies should provide follow-up info if previously provided info becomes outdated in a material way

Communications with Payors

Payor communications regarding investigational drugs

- Only applies to investigational drugs (*i.e.,* products not approved for any use)
- Pre-approval promotion is still prohibited
- No timing specified but there is some tension with the obligation to correct
- We recommend training on not so intuitive line between “scientific exchange” and unlawful pre-approval promotion

Disease awareness

Disease Awareness and "Help Seeking" Communications

- Draft 2004 FDA Guidance described disease awareness materials that are **not subject** to the labeling rules. Communications should:
  - Educate consumers/HCPs about a disease or health condition
  - Direct consumers to "see your doctor"
  - Omit any express or implied references to specific products; in other words: no drug names!
- Common pitfalls:

  (1) a company is the only manufacturer of a drug for a particular disease or health condition, or

  (2) the company only manufactures one product.
  - These infer a drug name such that a discussion by the company or about the disease will identify the drug
- **Pre-approval context not discussed in the guidance but is common within industry**
  - From an enforcement perspective, it is difficult to make a representation or suggestion about a drug that is not approved. Thus, pre-approval DA is low risk

Disease Awareness

Risks:

- Extensive materials or discussions about an investigational product implicitly identifies the drug, e.g. discussion of treatment or mechanism of action is so specific that the drug is clear
- In one-on-one setting (*e.g.,* office visits between MSLs and KOLs), the discussion or materials naturally lead to questions about product development
  - Why are you telling me this?
  - What is your company developing?
- Post-approval blending of enduring disease awareness materials and branded messaging through similar branding, colors, fonts, proximity of materials to ads, etc

Disease Awareness Enforcement

More risks from plaintiffs and State Attorney Generals than FDA

- FDA 2010 Warning Letter to **Novartis** about 2 educational websites
  - Discussed TKIs for first-line GIST and CML treatment, but Gleevec was the only TKI indicated for first-line treatment of GIST and chronic phase CML at the time
  - Design was visually similar to the Gleevec product website
  - Used embedded links that directed HCPs to the Gleevec product website and patients to a patient treatment website discussing Gleevec
- A handful of other letters have targeted drug that are alone in a class
- 2004 Draft Guidance was withdrawn but still represents OPDP "thinking"

- DA campaigns criticized for expanding health conditions inappropriately, e.g. restless leg
- State AGs have used state consumer protection laws to allege promotional intent (e.g., NY State/Purdue Settlement)
- Plaintiffs' bar alleges inappropriate behavior under consumer laws:
  - Jury decision against AbbVie for Androgel "Low T" campaign for $145M
  - Later overturned but not without huge legal effort and lots of bad press


GRANDMA, WHAT A BIG WHOOPING COUGH YOU HAVE.
Understand the danger your grandchild faces from whooping cough. It's a highly contagious disease that can be especially serious—even fatal—for infants. Unfortunately, many people who spread it may not know they have it.
If you have a new grandchild or one on the way, talk to your doctor or pharmacist about ways you can help protect yourself and your family from whooping cough, including getting vaccinated.
The Centers for Disease Control and Prevention (CDC) recommends everyone, including those around babies, make sure their whooping cough vaccination is up to date.
Ask your doctor or pharmacist if a whooping cough vaccination is right for you and your family.
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