OPDP Update on Oversight of Prescription Drug Promotion

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November 7, 2017

Topics

- Surveillance and Compliance Actions
- Guidance Updates

TUXARIN ER Warning Letter

- Webpage
- Indication:
  - TUXARIN ER 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 Limitation of Use**
    - Not indicated for pediatric patients under 18 years of age
- Boxed warning regarding respiratory depression and death which have occurred in children who received codeine following tonsillectomy and/or adenoidectomy
- Contraindications include postoperative pain management in children who have undergone tonsillectomy and/or adenoidectomy

Tuxarin ER®

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

- Long acting
- DEA Schedule III
- 40 mg codeine/chlorpheniramine combo tablet
- Minimize serious risk of over dosing
- No spills or taste issues
- Patent Protected-OB listable issued claims.

TUXARIN ER presentation

- Vast majority of patients with cough, cold & flu also have runny nose symptoms.
- Currently most codeine containing antitussives require four to six (4-6) times a day dosing.
- Chlopheniramine is an antihistamine that blocks histamine receptors. Histamine is a chemical that causes inflammation and sneezing. It 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.
- Chlorpheniramine is most widely used antihistamine to manage cough and cold symptoms.
- Issues with Hydrocodone and Chlorpheniramine commercial products
    - Current market is dominated by liquids prone to serious risk of dosing errors.
- Issues with Promethazine (antihistamine) plus Codeine commercial products.
    - Current market is dominated by short acting liquids that are prone to dosing errors.
    - FDA requires boxed warning added to all promethazine containing products
    - Unlike promethazine no known serious safety issues with Chlorpheniramine

TUXARIN ER Warning Letter

- Claims
  - Minimize serious risk of over dosing
  - Issues with Hydrocodone and Chlorpheniramine commercial products
    - Current market is dominated by liquids prone to serious risk of dosing errors
  - Issues with Promethazine (antihistamine) plus Codeine commercial products
    - Current market is dominated by short acting liquids that are prone to dosing errors
    - FDA requires boxed warning added to all promethazine containing products
    - Unlike promethazine no known serious safety issues with Chlorpheniramine
- Claims suggest that Tuxarin ER is safer than its competitors based on differences in dosage formulation and safety profiles of individual ingredients

TUXARIN ER Warning Letter

- Claims
  - 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
  - Chlorpheniramine is most widely used antihistamine to manage cough and cold symptoms
- Claims fail to adequately communicate the full approved indication
  - TUXARIN ER 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 Limitation of Use**
    - Not indicated for pediatric patients under 18 years of age

Draft Guidance on Medical Product Communications That Are Consistent With the FDA-Required Labeling – Questions and Answers

Purpose of Guidance

Provides FDA's thinking regarding when:

Communications that present information about a product that is not contained in the FDA-required labeling

Are considered to be consistent with the FDA-required labeling

What This Guidance Does

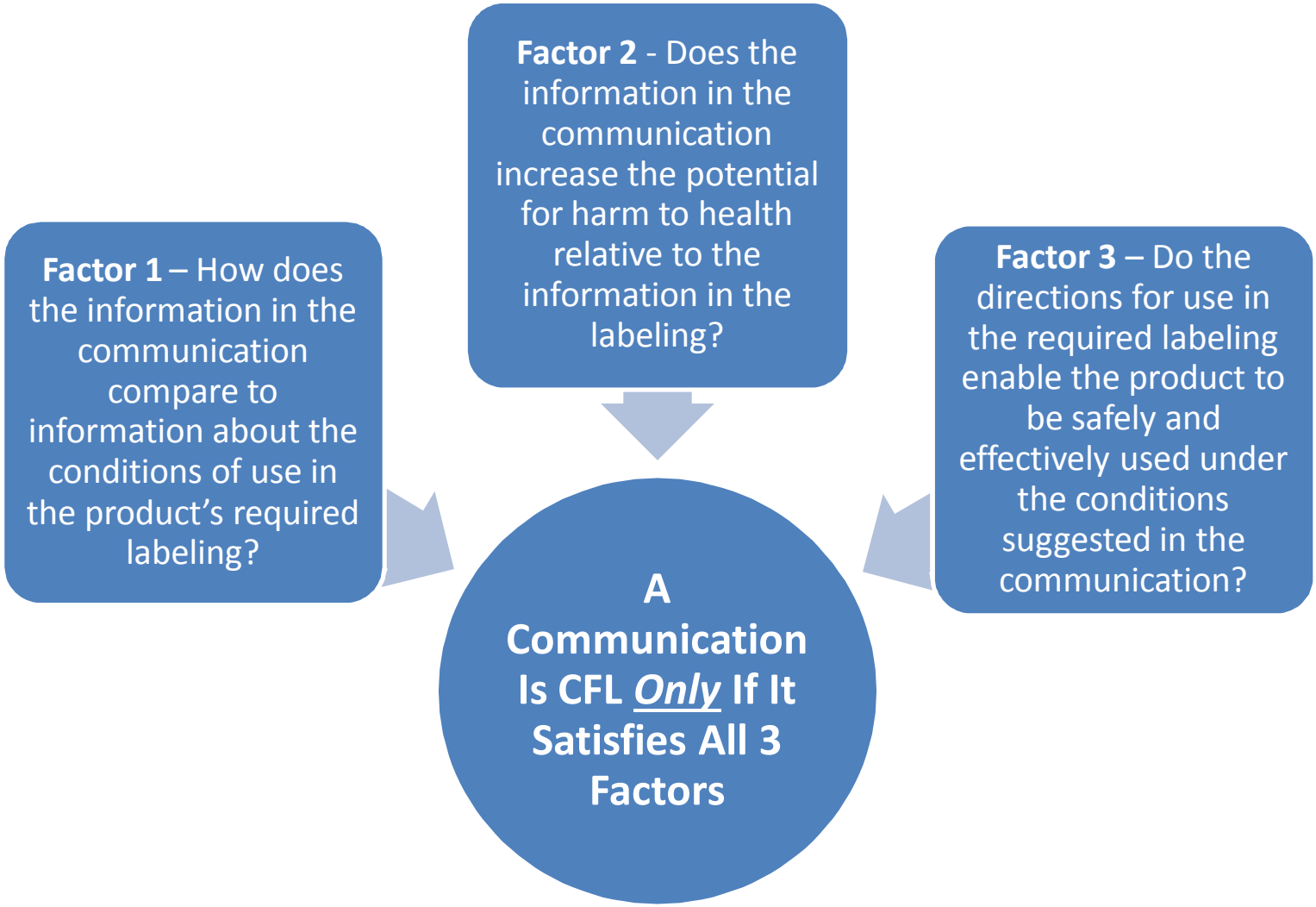
- **Describes how FDA determines whether a firm's communication is consistent with the FDA-required labeling (CFL)**
- **Clarifies for firms that FDA does not view CFL communications alone as evidence of a new intended use**
- **Provides general recommendations for conveying CFL information in a truthful and non-misleading way**

How Will FDA Assess Communications?

- **Guidance provides a 3-factor approach to evaluate whether a communication is consistent with the product's FDA-required labeling (CFL)**

- **FDA also evaluates whether FDA-regulated communications are truthful and non-misleading; the guidance provides recommendations for firms to consider when developing their presentations of information that is CFL**

The 3-Factor CFL Analysis



General Categories of Information That *Could* Be CFL

- Comparisons of the product's safety/efficacy to another product approved/cleared for the same indication
- Additional context about adverse reactions
- Information about the product's onset of action
- Information about the long-term safety/efficacy of products approved/cleared for chronic use
- Effects or use of a product in specific patient subgroups included in its approved/cleared population
- Patient-reported outcome information about the approved/cleared use
- Product convenience information, e.g., convenient dosing schedule
- Additional context about the mechanism of action described in the approved/cleared labeling

Not an Exhaustive List

General Categories of Information That Are Not CFL

Condition/disease is different than what the product is approved/cleared to treat

Use in patients outside of the approved/cleared population

Use of product for different stage, severity, or manifestation of disease than those for which the product is approved/cleared (i.e. not a subgroup)

Use of product as a monotherapy when it is only approved/cleared for use in conjunction with one or more therapies

Different route of administration or use in different tissue type than the approved/cleared route of administration or tissue type

Different strength, dosage, or use regimen than what is approved/cleared

Use of product in different dosage form than set forth in required labeling, e.g. capsule, solution

Not an Exhaustive List

A Communication Is Determined to Be CFL… Now What?

Considerations for Truthful and Non-misleading CFL Communications

- **Recommendations for truthful and non-misleading communications of CFL information are outlined in the guidance, including recommendations regarding evidentiary support**
- **Communications that lack appropriate evidentiary support are likely to be false or misleading, and can cause patient harm**
- **FDA will not consider a communication to be misleading based only on the lack of evidence sufficient to satisfy the applicable approval/clearance evidentiary standard**

Considerations for the Evidentiary Support of CFL Communications

- **To be truthful and non-misleading, representations or suggestions need to be:**
  - **Grounded in fact and science**
  - **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 the CFL communication**
  - **FDA would not consider representations or suggestions in a CFL communication to be false or misleading based only on the lack of evidence sufficient to satisfy the applicable approval/clearance standard**
- **If a communication relies on a study that is inadequate to support the representations/suggestions presented, disclosing the limitations of the study does not correct the misleading message**

Anything Else?

- **FDA-regulated promotional materials must also comply with other applicable requirements of the Food, Drug & Cosmetic Act and implementing regulations**
  - **E.g., for prescription drugs, appropriate disclosures of risk information, fair balance**

Themes From the Docket Comments

- Clarify or revise the 3-factor analysis
- Provide additional examples
- Clarify existing examples
- Revise or clarify the evidence standard of scientifically appropriate and statistically sound
- Revise or further explain the disclosure recommendations

Draft Guidance on Drug and Device Manufacturer Communications with Payors, Formulary Committees, and Similar Entities – Questions and Answers

Purpose of Guidance

To provide answers to common questions regarding firms' communications with payors, formulary committees, and similar entities regarding the following:

- **Health care economic information** (HCEI) regarding approved prescription drugs
- Certain information regarding **investigational drugs and devices** (not yet approved/cleared for <u>any</u> use)

Communication of HCEI to Payors Regarding Approved Drugs

Brief Background

Sec. 502(a) of the FD&C Act: False or misleading labeling

1997

FDAMA sec. 114

Amended sec. 502(a) to include a provision regarding the communication of HCEI to payors about approved drugs

2016

21st Century Cures Act

Further amended HCEI provision in sec. 502(a)

What does this guidance do?

Health Care Economic Information:

- Provides FDA's recommendations for how firms can communicate HCEI about approved drugs to payors in accordance with section 502(a) of the FD&C Act.

Section 502(a) FAQs

"What is considered to be a formulary committee or similar entity?"

"How is HCEI defined?"

"What does it mean to relate to an approved indication?"

"What is 'competent and reliable scientific evidence?'"

Sec 502(a) Key Concepts

Section 502(a):

- **"Health care economic information 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, **shall not be considered to be false or misleading** under this paragraph if the health care economic information **relates to an [approved] indication**…for such drug, is based on **competent and reliable scientific evidence**, and includes, where applicable, a **conspicuous and prominent statement describing any material differences between the health care economic information and the [approved] labeling**. . ."

Sec 502(a) Key Concepts

Scope of audience for HCEI:

- **Payors, formulary committees, or other similar entities**
  - With "knowledge and expertise in the area of health care economic analysis[1]" in "carrying out its responsibilities for the selection of drugs for coverage or reimbursement[1]" on a population basis
  - Expertise is necessary to understand the methods and limitations of HCEI
- This guidance does **not** apply to communications to other audiences, such as health care professionals or consumers

[1] Section 502(a) of the Federal Food, Drug, and Cosmetic Act

Sec 502(a) Key Concepts

HCEI must relate to an approved indication:

- Should relate to the disease/condition, manifestation of the disease/condition, or symptoms associated with the disease/condition in the indicated patient population
- Examples of HCEI that relate to the approved indication:

Duration of treatment	**Length of Hospital Stay**
Practice Setting	**Validated Surrogate Endpoints**
Burden of Illness	**Clinical Outcome Assessments**
Dosing	**Persistence**
Patient Subgroups	**Comparisons**

Sec 502(a) Key Concepts

Examples of HCEI that are not considered to relate to the approved indication:

- A drug is indicated for the acute relief of angina
  - HCEI discusses effect of the drug on delaying the worsening of coronary artery disease
  - **Disease course modification → not related to approved indication**

Sec 502(a) Key Concepts

Evidentiary Standard:

- HCEI shall not be considered false or misleading if, among other things, it is "based on **competent and reliable scientific evidence**."
  - Amount and type of evidence is dependent on HCEI being presented
  - FDA will consider:
    - Generally-accepted scientific standards that yield accurate and reliable results
    - Current good research practices
  - Applies to all components of HCEI, including economic consequences and clinical outcomes

Sec 502(a) Key Concepts

Conspicuous and prominent statement:

- If HCEI includes material differences from the FDA-approved labeling → **a conspicuous and prominent statement describing any material differences** between the health care economic information and the approved labeling must be presented
- Firms should not misleadingly represent that the clinical assumptions that vary from the FDA-approved labeling have been found by FDA to be safe and effective

Guidance Recommendations

Include Material Information:

- Study design and methodology
- Generalizability
- Limitations
- Sensitivity analysis
- Information for balanced and complete presentation
  - FDA-approved indication/labeling
  - Disclosure of omitted studies or data sources
  - Risk information
  - Financial/affiliation biases

Key Concepts

Section 502(a):

". . .For purposes of this paragraph, the term '**health care economic information**' means 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.

Such analysis **may be comparative to the use of another drug, to another health care intervention, or to no intervention**….Such term does not include any analysis that relates only to an indication that is not approved under section 505 or under section 351 of the Public Health Service Act for such drug.”

Communication to Payors Regarding Investigational Drugs and Devices

What does this guidance do?

Investigational Drugs and Devices:

- Provides FDA's current thinking on the communication to payors about investigational products*

*** "Investigational products" in this guidance refers to drugs and devices that must be approved/cleared to be legally marketed, but are not yet approved/cleared by FDA for any use**

Key Concepts

Types of Information:

- Product information
- Information about the indication sought
- Factual presentations of results from clinical or preclinical studies
- Anticipated timeline for possible FDA approval/clearance
- Product pricing information
- Targeting/marketing strategies
- Product-related programs/services

Key Concepts

Additional Recommendations:

- Info should be unbiased, factual, accurate, and non-misleading
- Provide a clear statement that the product is under investigation and that the safety or effectiveness of the product has not been established
- Provide information related to the stage of product development
- Provide follow-up information if previously communicated information becomes outdated due to significant changes or new information

➢ **Representation that an investigational product is FDA-approved/cleared or otherwise *safe* or *effective* for the purpose(s) for which it is under investigation would <u>not</u> be appropriate.**

Themes From the Docket Comments

- Clarify the definition of HCEI
- Clarify or revise the scope of audience
- Clarify or revise the disclaimers/disclosures
- Expand to include communications about unapproved uses of approved/cleared products

OPDP Web Resources

- OPDP Home Page
  - http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm090142.htm
- Guidances
  - http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm109905.htm#Guidances
- Social Science Research
  - https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm090276.htm
- Warning and Untitled Letters
  - www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCcompanies/default.htm

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