U.S. FOOD & DRUG ADMINISTRATION

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

Guidance for Industry

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Agenda

- **Purpose of the Guidance**
  - **Scope: Applies to drugs and medical devices for humans, and animal drugs**
- **Description of what the guidance does/does not do**
- **Overview of guidance:**
  - **Overview of the 3-factor consistent with FDA-required labeling (CFL) analysis**
  - **Overview of considerations for truthful and non-misleading CFL promotional communications**
- **Summary of changes from the draft guidance**

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 product communication is consistent with the FDA-required labeling**

- **Clarifies for firms that FDA does not intend to rely on product communications that are determined to be CFL to establish a new intended use, different from the use(s) for which the product is legally marketed**

- **Provides general recommendations for conveying CFL promotional communications in a truthful and non-misleading way**

What This Guidance Does Not Do

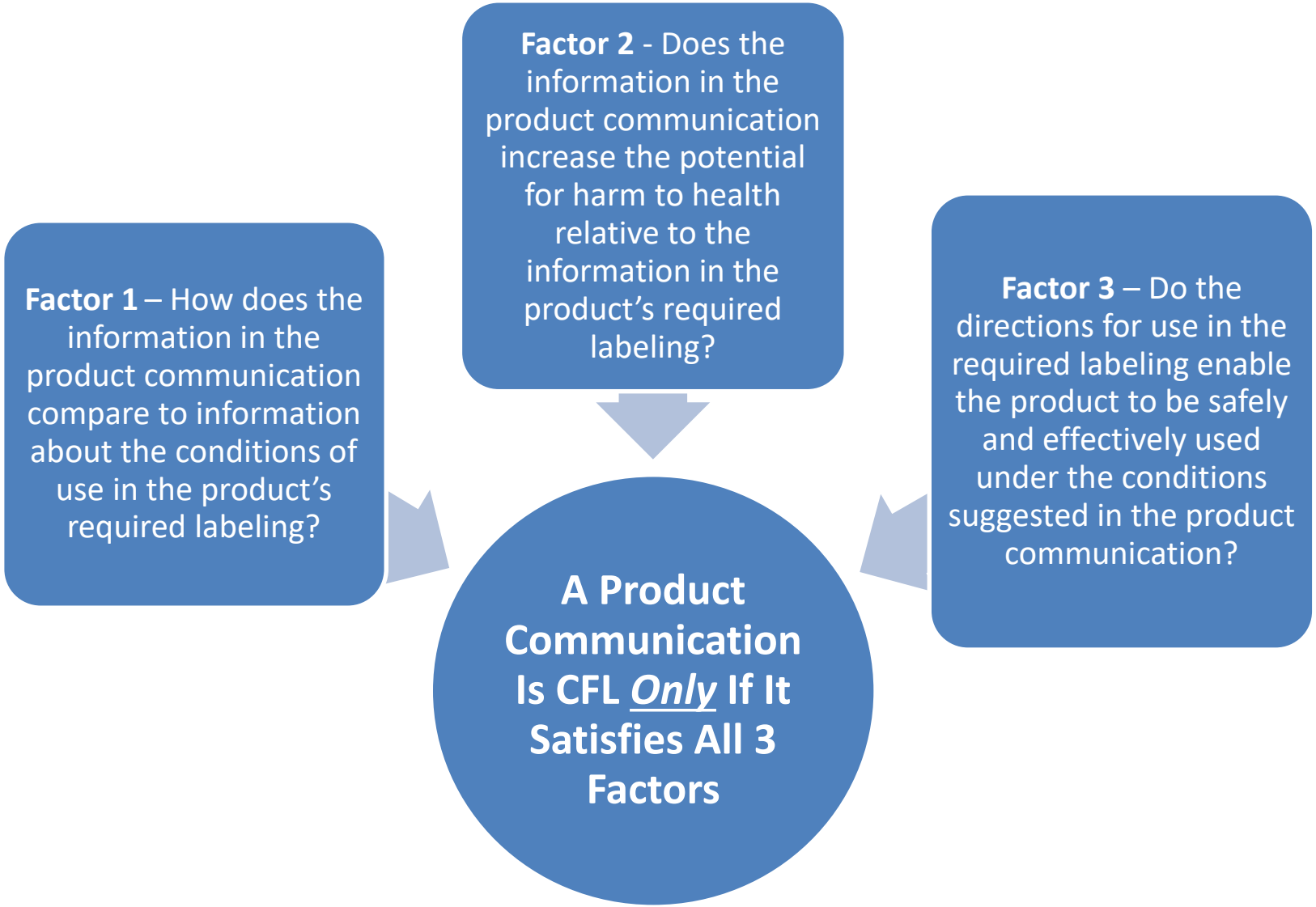
- **Provide recommendations regarding communications about unapproved uses of FDA approved or cleared medical products**
- **Relieve firms of obligations to comply with other applicable requirements**
- **Change a firm's existing obligations to update its FDA-required labeling to ensure that the labeling is not false or misleading, or for other reasons**

How Will FDA Assess Communications?

- **FDA uses a 3-factor approach to evaluate whether a product 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 CFL promotional communications**

The 3-Factor CFL Analysis



Factor 1: Comparison of Information in the Product Communication to the Product's FDA-Required Labeling

Elements	If NO,	If YES,
Do the representations/suggestions in the communication relate to a different indication than the one(s) in the required labeling?	Continue analysis	Not CFL
Is the patient population represented/suggested in the communication outside of the approved patient population in the required labeling?	Continue analysis	Not CFL
Do the representations/suggestions in the communication conflict with the use limitations or directions for handling, preparing, and/or using the product reflected in the required labeling?	Continue analysis	Not CFL
Do the representations/suggestions about the product conflict with the recommended dosage or use regimen, route of administration, or strength(s) (if applicable) set forth in the required labeling?	Continue analysis	Not CFL

Factor 2: Does the Product Communication Increase the Potential for Harm to Health Relative to the Labeling?

- **If using of the product in accordance with the product communication would reasonably be expected to introduce new risks or materially increase the rate of occurrence or severity of existing risks included in the FDA-required labeling, the product communication is not CFL**
  - **This includes potential for harm from abuse or misuse, or the potential for harm to the health of humans from certain animal drug uses, or the potential for harm to health from secondary exposure to certain medical products**

Factor 3: Do the Directions for Use in the Labeling Enable the Product to Be Safely and Effectively Used?

- **Does the product's required labeling provide the necessary information to use the product safely and effectively under the conditions suggested in the product communication?**
  - **Does required labeling include sufficient information about potential or expected risks and effects of using the product as presented in the communication?**
  - **Does required labeling include appropriate context for unique considerations associated with using the product as suggested by the communication?**

General Categories of Information That *Could* Be CFL

- Comparisons of the product's safety/efficacy to another product approved 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 for chronic use
- Effects or use of a product in specific patient subgroups included in its approved population
- Information concerning the effects of the product on the patient for its FDA-approved indication in its approved patient population
- Product convenience information, e.g., convenient dosing schedule
- Additional context about the mechanism of action described in the required labeling
- Information about the tolerability of a product when used concomitantly with another product for a co-morbid condition

Not an Exhaustive List

General Categories of Information That Are Not CFL

- Condition/disease is different than what the product is approved to treat
- Use in patients outside of the approved population
- Use of product for different stage, severity, or manifestation of disease than those for which the product is approved
- Use of product as a monotherapy when it is only approved for use in conjunction with one or more therapies
- Different route of administration or use in different tissue type than the approved route of administration or tissue type
- Different strength, dosage, or use regimen than what is approved
- Use of product in different dosage form than set forth in required labeling, (e.g. approved as capsule; communication about solution)

Not an Exhaustive List

A Promotional Communication Is Determined to Be CFL… Now What?

Considerations for Truthful and Non-misleading CFL Promotional Communications

- **Recommendations for truthful and non-misleading CFL promotional communications are outlined in the guidance, including recommendations regarding evidentiary support**

- **CFL promotional communications that lack appropriate evidentiary support are likely to be false or misleading, and can cause patient harm**

- **FDA will not consider a CFL promotional communication to be false or misleading based only on the lack of evidence sufficient to satisfy the applicable approval/clearance standard**

Considerations for the Evidentiary Support of CFL Promotional 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 promotional communication**
  - **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**
  - **The amount and type of evidence needed to support a particular CFL promotional communication depends in part on the topic addressed by the communication**

- **If a CFL promotional communication relies on a study that is inadequate to support the representations/suggestions presented in the promotional communication, disclosing the limitations of the study does not correct the misleading message**

Advice to Help Ensure that a CFL Promotional Communication is Truthful and Non-misleading

- **Accurately represent the study results or other data and information that are relied upon to support the CFL promotional communication**
  - **Clearly and prominently present material aspects of the study design and methodology**
  - **Clearly and prominently disclose the material limitations related to the study design, methodology, and results**
- **Accurately characterize and contextualize the relevant information about the product**
  - **Disclose unfavorable or inconsistent findings**
  - **Accurately characterize the limitations of the strength of the evidence and the conclusions that can be drawn from it**
- **If the FDA-required labeling contains data or information related to what is being represented/suggested in the CFL promotional communication, include the data or information from the FDA-required labeling in a clear and prominent way**

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**

Practical Considerations

- **For firms voluntarily submitting promotional materials that contain claims or presentations that are potentially CFL for OPDP review**
  - **Follow the established advisory request process**
  - **Provide annotated references to support the claims and presentations in the promotional materials**

Changes from the Draft Guidance

- Clarifies the scope of communications covered by the guidance
- Explains factors 2 and 3 of the CFL analysis and includes examples to illustrate their application
  - Also explains that for devices that are 510(k)-cleared or -exempt, firms should refer to existing device regulations and guidance and need not separately analyze under the factors discussed in Q2/A2
- Expands on the categories and examples of information that could be CFL
- Clarifies recommendations for truthful and non-misleading CFL promotional communications

Contact Information

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

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Overview

- Guidance background
- Communications of health care economic information (HCEI) for approved drugs
  - Definition
  - Key concepts
  - Guidance Recommendations
- Communications of HCEI for approved/cleared medical devices
- Communications regarding unapproved products and unapproved uses of approved/cleared medical products

Guidance Development

- Developed by a cross-Agency working group
  - Representation from CDER, CBER, CDRH, OCC, Office of Policy
- Considered wide range of information, including:
  - Stakeholder feedback
  - Published literature

Guidance Development (cont.)

- Draft guidance published January 19, 2017
  - Comment period closed April 19, 2017
- Received 23 comment submissions
  - 10 drug associations
  - 4 each from payor and policy organizations
  - 2 each from pharmacy and multi-organizations
  - 1 from the general public
  - Themes: definition of HCEI, scope of audience, background/contextual information, and preapproval communications
- **Final guidance published June 12, 2018**

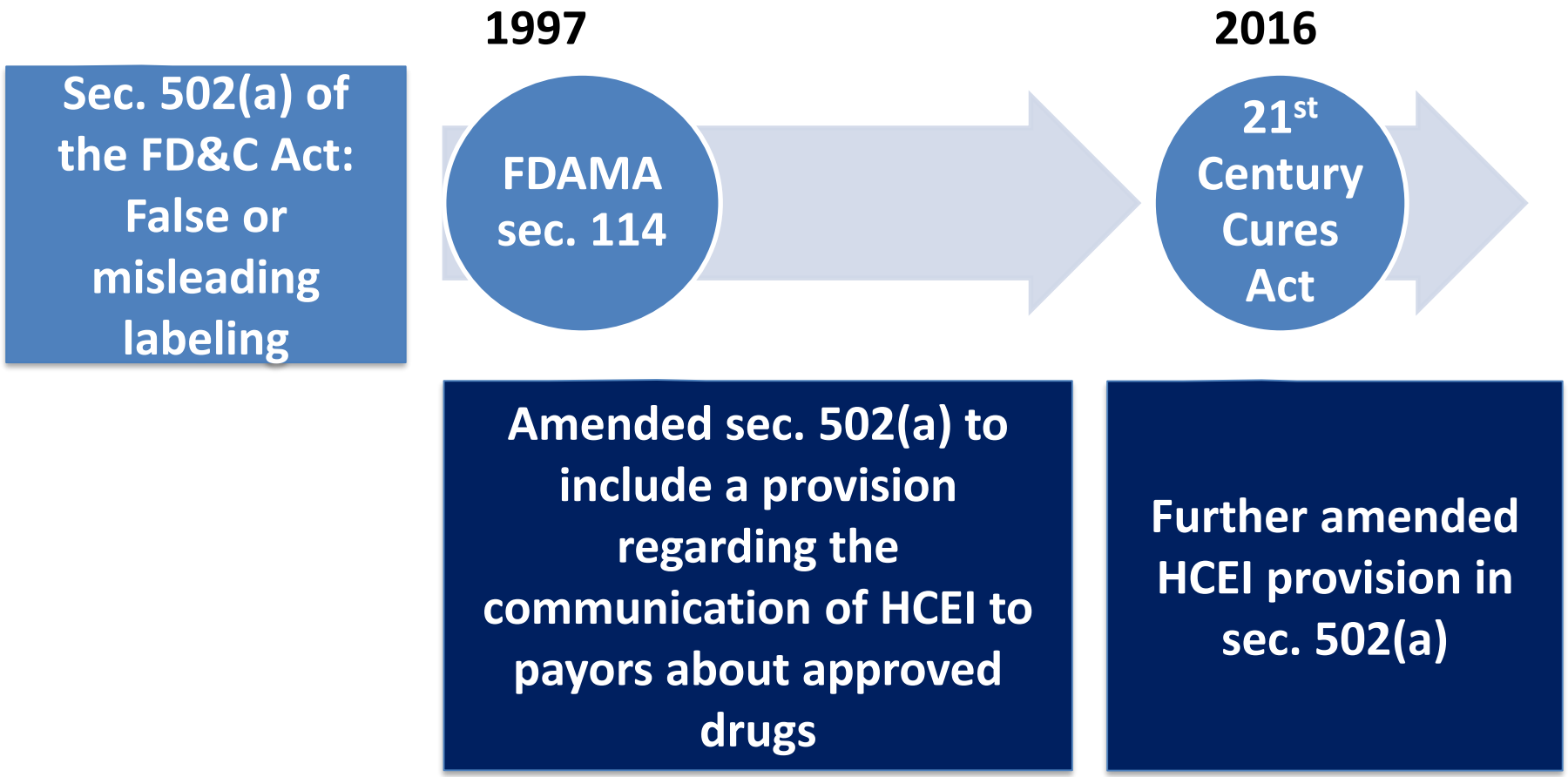
Purpose of Guidance

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
- **HCEI** regarding **approved/cleared medical devices**
- Communications regarding unapproved products and **unapproved uses of approved/cleared medical products**

Communication of HCEI to Payors Regarding Approved Drugs

Brief Background



What does this guidance do?

Health Care Economic Information (HCEI):

- 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?'"

HCEI Definition

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.

HCEI Definition (cont.)

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.”

HCEI Definition (cont.)

- Includes monetary costs and resource utilization*
  - Related to clinical outcomes of treating, preventing or diagnosing a disease
- Can be presented in a variety of ways*
  - Evidence dossier
  - Reprint of a publication from a peer-reviewed journal
  - Slide presentation
  - Payor brochure
  - Software package comprising a model with a user manual

**These are examples; the list is not meant to be all inclusive.*

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

Key Concepts (cont.)

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. . .”

Scope of Audiences

Payors, formulary committees, or other similar entities

- Possess knowledge and expertise in the area of health care economic analysis[1]
- Perform selection or acquisition of drugs for coverage or reimbursement on a population basis on behalf of a health care organization
- Have range of expertise in multiple disciplines and established procedures for carefully considering evidence about medical products

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

Scope of Audiences (cont.)

- Includes public and private payors
- Recommendations do not apply to communications to other audiences, such as health care professionals or consumers
- Does include health care professionals that have multiple roles
  - HCP who serves on a formulary committee and provides care to individual patients would fall within the scope of the guidance when performing professional responsibilities for a payor regarding the selection of drugs for coverage or reimbursement

Scope of Information

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
- 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
  - Encompasses aggregate information for all patients using a drug, even if a subset is outside of the approved indicated population

Scope of Information

Examples of HCEI that relates to an approved indication:

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

Examples NOT Related

- HCEI analyses regarding the use of the drug to prevent, cure, or mitigate/change the course of the disease, when the drug is only approved to relieve symptoms of the disease
  - Example: An HCEI analysis for a drug indicated for the management of pain in cancer patients that discusses the effect of the drug on prolonging patient survival

Examples NOT Related (cont.)

- HCEI analyses derived from studies limited to patient populations that are not within the indicated patient population
  - Example: An HCEI analysis of the treatment in patients outside of the indicated age group when the drug is approved only for use in patients in a certain age group

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

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
- Examples of material differences:
  - New or increased risks
  - Different dosing/use regimens
  - Different endpoints
  - More limited/targeted patient populations

Guidance Recommendations

Include Material Information (Examples):

- 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

Guidance Recommendations

Presentation of Material Information:

- Can be concise, as long as all material information is provided
- Present contextual information in conjunction with the information within the HCEI to which it relates
  - Or include a prominent reference within the HCEI presentation to where the contextual information can be found
- Do not need duplicative disclosures
  - Information is provided in accordance with recommendations from authoritative bodies

Guidance Recommendations

Example of Presentation:

- An HCEI presentation is based on real-world data where actual patient use of the drug falls outside of the recommended dosing/use regimen in FDA-approved labeling
- Presentation should include a statement, “The dosing regimen used in this study varies from the dosing regimen in the FDA-approved labeling”
  - In direct conjunction with HCEI presentation
  - Similar/comparable font style, size and contrast

Guidance Recommendations

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.

Submissions to FDA

- HCEI disseminated in accordance with sec 502(a) is **promotion** and subject to FDA's requirements for submission of promotional materials.
  - Post-marketing requirement:
    - 21 CFR 314.81(b)(3)(i)
    - Form FDA 2253: code as "Formulary Economic"
  - Pre-dissemination submission of promotional materials for accelerated approval drugs or drugs approved based on animal studies:
    - 21 CFR 314.550, 314.640, 601.45, and 601.94

Communication to Payors Regarding Approved or Cleared Medical Devices

What does this guidance do?

Health Care Economic Information (HCEI):

- Provides FDA's recommendations for how firms can communicate HCEI about approved or cleared medical devices to payors

HCEI for Devices

- Several commenters suggested applying recommendations to medical devices.
- FDA believes recommendations provided for drugs are applicable to device firms' communications to payors.
- Section III.B was added to the guidance.

HCEI for Devices (cont.)

- Recommendations for “drugs” in section III.A generally apply to
  - “devices”
  - “approved/cleared indications/uses”
  - “FDA-required labeling”
- Must not be false or misleading
- Not subject to same postmarketing requirements as drugs to submit promotional materials

Communications by Firms to Payors Regarding Unapproved Products and Unapproved Uses of Approved/Cleared Products

What does this guidance do?

Unapproved Products:

- Provides FDA's current thinking on communications by firms to payors about unapproved products
- Includes drugs and medical devices not yet approved/cleared/licensed by FDA for any use

Unapproved Uses of Approved/Cleared/Licensed Products:

- Provides FDA's current thinking on communications by firms to payors regarding unapproved uses of their approved drugs and cleared/licensed medical devices

Key Concepts

- Types of information
- Recommendations
- Inappropriate communications
- Additional considerations

Types of Information

- Product information
  - Drug class, device description
- Information about the indication sought
  - Information from clinical study protocol(s) about endpoints and patient populations
- Anticipated timeline for possible FDA approval/clearance/licensure of the product or new use

Types of Information (cont.)

- Product pricing information
- Patient utilization projections
- Product related programs or services
- Factual presentations from results of studies
  - Clinical studies of drugs or devices
  - Bench tests that describe device performance
  - No characterizations/conclusions about safety or effectiveness

Recommendations

- Should be unbiased, factual, accurate, and non-misleading
- Provide a clear statement that the product/use is not approved/cleared/licensed and that the safety or effectiveness of the product or use has not been established
- Provide information related to the stage of product development, including status of submission of marketing application
- Provide follow-up information if previously communicated information becomes outdated

Recommendations (cont.)

- For communications that include factual presentations from studies
  - Describe the material aspects of study design/methodology, including material limitations
  - Do not selectively present results
- For unapproved uses of approved/cleared/licensed products
  - Include a prominent statement disclosing the indication(s) for which FDA has approved/cleared/licensed the product
  - Disseminate with a copy of most current FDA-required labeling

Inappropriate Communications

- Communications between firms and payors that represent that an unapproved product is FDA-approved/cleared/licensed or has otherwise been determined safe or effective for the purpose(s) being studied would not be appropriate.

- Communications between firms and payors that represent that an unapproved use of an approved/cleared/licensed product is FDA-approved/cleared/licensed or that the product is safe or effective for the use(s) for which it is being studied would not be appropriate.

Additional Considerations

If recommendations in the guidance are followed:

- FDA does not intend to enforce any applicable post-marketing submission requirements for these materials.
- FDA does not intend to object to such communications under 21 CFR 312.7(a) or 21 CFR 812.7(a).
- FDA does not intend to use such communications as evidence of a new intended use.

THANK YOU!

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