



Regulatory Education  
for Industry (REdI):

## **PRESCRIPTION DRUG LABELING - CHALLENGES AND ISSUES**

Bethesda Marriott | Pooks Hill, MD | November 3-4, 2015

# **Drug Labeling and Its Impact on Promotion**

Office of Prescription Drug Promotion (OPDP)  
Food and Drug Administration

Office of Promotion and Advertising Review  
Merck & Co., Inc.



# Drug Labeling and Its Impact on Promotion

## Moderator

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# **PRESCRIPTION DRUG LABELING - CHALLENGES AND ISSUES**

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# **Drug Labeling and Its Impact on Prescription Drug Promotion**

**CDR Aline Moukhtara**  
Regulatory Review Officer

**CDR Elaine Hu Cunningham**  
Senior Advisor for Evidence Review

Office of Prescription Drug Promotion (OPDP)  
Food and Drug Administration



# OPDP's Mission and Objectives

- **Mission**

- Protect the public health by ensuring that prescription drug information is truthful, balanced, and accurately communicated

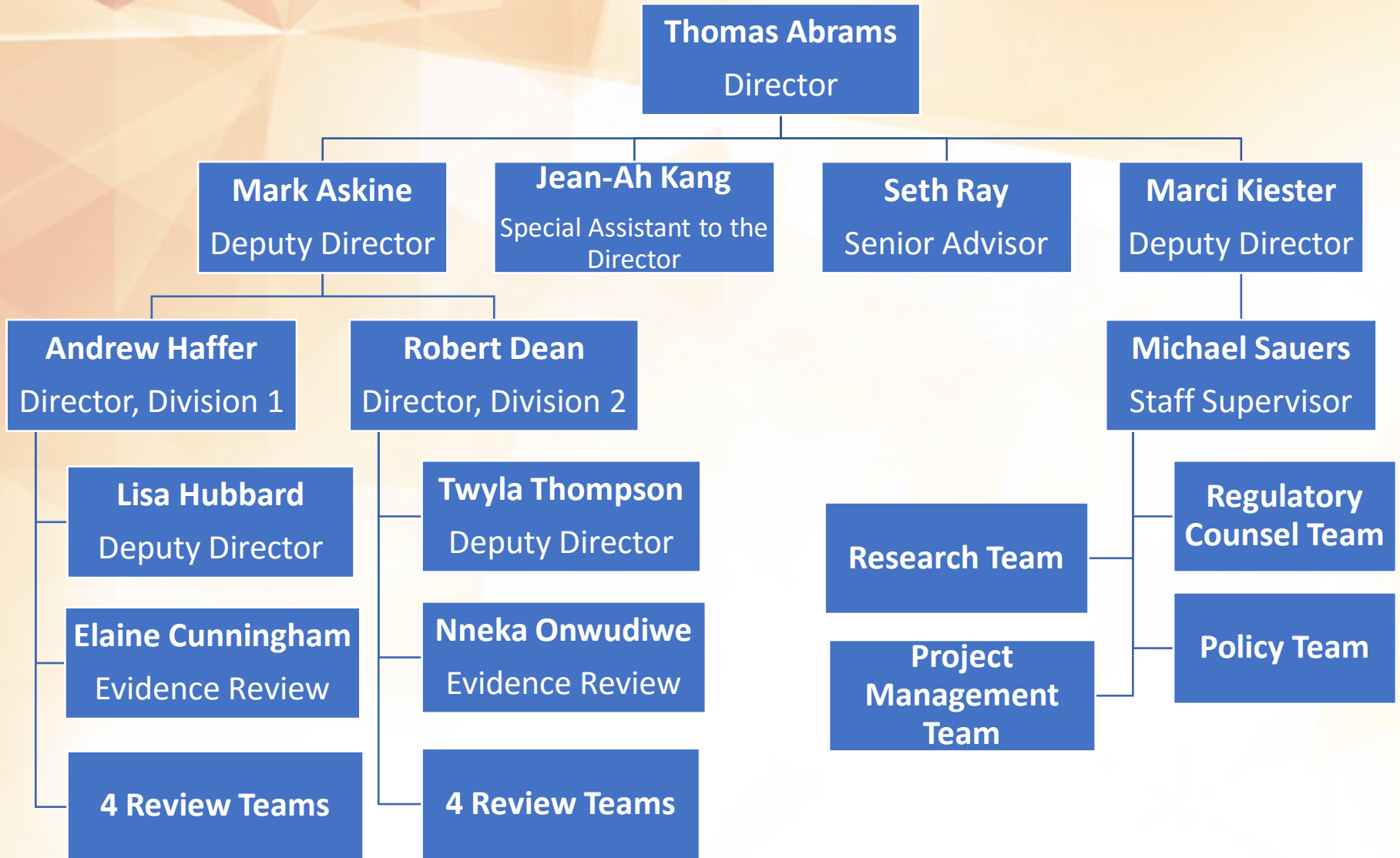
- **Objectives**

- Ensure that prescription drug promotion is not false or misleading
- Ensure that balanced picture of drug is conveyed
- Aid in the communication of more useful information about drugs and diseases to the American public





# OPDP Organization Chart





# OPDP's Role

- Compliance with Federal Food Drug & Cosmetic Act and Code of Federal Regulations
- Advice to industry and within FDA
- Surveillance
- Guidances and policy development
- Research
- Enforcement



# Bad Ad Program

- FDA-sponsored outreach program designed to increase awareness of healthcare professionals (HCPs) about the role they can play in helping FDA ensure that prescription drug promotion is truthful and not misleading
- When HCPs have concerns about prescription drug promotion, they can report it to FDA:
  - Call
    - **855-RX-BadAd**
  - E-mail
    - [BadAd@fda.gov](mailto:BadAd@fda.gov)
- Continuing Education Program for HCPs
  - Physicians, pharmacists, nurses, physician assistants, nurse practitioners



# Regulations

## Prescription Drug Advertising (21 CFR 202.1)

- Not be false or misleading
- Consistent with FDA-approved product labeling
- Supported by an appropriate level of evidence
- Present a fair balance between efficacy and risk information
- Reveal facts material with respect to consequences that may result from the use of the drug as recommended or suggested





# Regulations

## Requirements on content and format of labeling for human prescription drug and biological products

**(21 CFR 201.56(a)(2))**

“ . . . . The labeling must be informative and accurate and neither promotional in tone nor false or misleading in any particular. . . . ”



# OPDP's Role in Product Labeling

- OPDP reviews draft drug labeling for promotional implications, in collaboration and consultation with various entities within the FDA.
- Labeling is a critical component for prescription drug promotion.



# Product Labeling and Prescription Drug Promotion

- The FDA-approved product labeling is an integral part for reviewing proposed promotional materials when Sponsors request advisory comments, and for evaluating promotional claims in the public domain.



# TussiCaps<sup>®</sup> Product Labeling and Enforcement Example

- **Warning Letter** (July 27, 2015, professional sales aid)
- **Indication**
  - For relief of cough and upper respiratory symptoms associated with allergy or a cold in adults and children 6 years of age and older
- **Contraindications**
  - Patients with a known allergy or sensitivity to hydrocodone or chlorpheniramine
  - Children less than 6 years of age due to the risk of fatal respiratory depression





# TussiCaps® Product Labeling and Enforcement Example

- **Warnings**

- Respiratory depression, head injury and increased intracranial pressure, acute abdominal conditions, obstructive bowel disease, and pediatric use

- **Precautions**

- Patients with narrow-angle glaucoma, asthma, or prostatic hypertrophy, elderly or debilitated patients, and patients with severely impaired hepatic or renal function, hypothyroidism, Addison's disease, or urethral stricture



# TussiCaps® Product Labeling and Enforcement Example

- TussiCaps is associated with drug abuse and dependence.
- Adverse Reactions: nausea and vomiting, sedation, drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, dizziness, psychic dependence, mood changes, and dose-related respiratory depression, which has been associated with death



# TussiCaps® Product Labeling and Enforcement Example

**TussiCaps**  
Hydrocodone polistirex  $\text{CIII}$   
Chlorpheniramine polistirex  
extended-release capsules

Full-Strength 10 mg/8 mg    Half-Strength 5 mg/4 mg

For the relief of cough and upper respiratory symptoms associated with colds or allergies

ECR 10/CP 10/8    ECR 5/CP 5/4

**TUSSICAPS** provides powerful, sustained, and affordable cough and cold relief in a capsule

Confidence Guaranteed


- **Omission of material facts**
  - **For the relief of cough and upper respiratory symptoms associated with colds or allergies**
    - **Omission of “in adults and children 6 years of age and older”**





# TussiCaps® Product Labeling and Enforcement Example

**TussiCaps**  
Hydrocodone polistirex ©  
Chlorpheniramine polistirex  
extended-release capsules  
Full-Strength 10 mg/4 mg    Half-Strength 5 mg/4 mg



**Powerful Relief**

- Efficacious, safe, and proven combination of ingredients provide cough and cold symptom relief


Each extended-release TUSSICAPS capsule contains the equivalent of

	Full-Strength	Half-Strength
<b>Hydrocodone bitartrate</b>	<b>10 mg</b>	<b>5 mg</b>
<b>Chlorpheniramine maleate</b>	<b>8 mg</b>	<b>4 mg</b>

in a polistirex formulation that provides for twice-daily dosing  
— Decongestant-free, sugar-free —

**Sustained Relief**

- Extended relief from uncontrolled coughs eliminates the need for middle of the night dosing
- TUSSICAPS is dosed every 12 hours



- Image of coughing young child
- Contraindicated in children < 6 years of age due to the risk of fatal respiratory depression
- PI also indicates that caution should be exercised when administering to pediatric patients  $\geq$  6 years of age





# TussiCaps® Product Labeling and Enforcement Example

## Powerful Relief

- Proven combination of ingredients that are effective and safe

Each extended-release TUSSICAPS capsule contains the equivalent of

	Full-Strength	Half-Strength
Hydrocodone bitartrate	10 mg	5 mg
Chlorpheniramine maleate	8 mg	4 mg

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## Sustained R

- TUSSICAPS 12
- the need for n

## Affordable Money Back

PAY NO MORE

BUPAP®

TUSS

BIN: 610020 GROUP: C

Now With a Money Back Guarantee!

\*This offer will buy the out-of-pocket cost down to \$25 provided the minimum and maximum. Offer may be used more than once and for all products listed. See reverse side for additional details.

## Patient Preferred Capsule

- Convenient
- Accurate

“This brochure is the property of ECR Pharmaceuticals and is to remain in the representative’s possession. Appropriate product labeling should accompany discussion with the healthcare professionals and distribution of product samples.”

**Usual Dosage:** One full-strength or half-strength capsule every 12 hours, depending on age, for patients six years of age and older. Do not exceed two capsules in 24 hours.



ECR Pharmaceuticals  
Richmond, VA 23255

This brochure is the property of ECR Pharmaceuticals and is to remain in the representative’s possession. Appropriate product labeling should accompany discussions with the healthcare professionals and distribution of product samples.

DTUS3B – REV SEP 2013



# TussiCaps<sup>®</sup> Product Labeling and Enforcement Example

- **Omission of Risk**

- Fails to include **any** risk information despite numerous efficacy claims
- Statements at the bottom of last page:
  - “This brochure is the property of ECR Pharmaceuticals and is to remain in the representative’s possession. Appropriate product labeling should accompany discussions with the healthcare professionals and distribution of product samples.”
  - This does not mitigate the omission of risk.
- By failing to present any information regarding the risks, including serious and potentially fatal risks, the sales aid is misleading because it suggests that TussiCaps is safer than has been demonstrated, and is especially concerning in its potential impact on the public health.



# Brovana<sup>®</sup> Product Labeling and Enforcement Example

- **Indication**

- Long-term, twice daily (morning and evening) maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. BROVANA Inhalation Solution is for use by nebulization only.

- **Important Limitations of Use**

- Brovana is not indicated to treat acute deteriorations of COPD.
- Brovana is not indicated to treat asthma. The safety and effectiveness of Brovana in asthma have not been established.





# Brovana<sup>®</sup> Product Labeling and Enforcement Example

- **Boxed Warning**
  - Asthma-related death
- **Contraindications**
  - Patients with history of hypersensitivity to arformoterol, racemic formoterol, or to any other components of Brovana
  - Patients with asthma without the use of a long-term asthma control medication





# Brovana<sup>®</sup> Product Labeling and Enforcement Example

- **Warnings and Precautions**
  - Deterioration of disease and acute episodes, excessive use of Brovana and use with other Long-Acting Beta2-Agonists (LABA), paradoxical bronchospasm, cardiovascular effects, coexisting conditions, hypokalemia and hyperglycemia, and immediate hypersensitivity reactions
- **Adverse Reactions (most common)**
  - Pain, chest pain, back pain, diarrhea, sinusitis, leg cramps, dyspnea, rash, flu syndrome, peripheral edema, and lung disorder



# Brovana<sup>®</sup> Product Labeling and Enforcement Example

If you have COPD,  
Are you using your nebulizer  
sometimes 4 or more times a day?

If so, talk to your doctor, and see if you can

Go to see  
the family

#### INDICATION

BROVANA<sup>®</sup> (arformoterol tartrate) Inhalation Solution is a medicine called a long-acting beta<sub>2</sub>-agonist or LABA. BROVANA is used long term, twice a day (morning and evening), in controlling symptoms of chronic obstructive pulmonary disease (COPD) in adults with COPD. BROVANA is for inhalation use only through a standard jet nebulizer connected to an air compressor and should not be swallowed or injected.

#### IMPORTANT PATIENT INFORMATION

People with asthma who take long-acting beta<sub>2</sub>-adrenergic agonist (LABA) medicines such as BROVANA have an increased risk of death from asthma problems. It is not known if LABA medicines, such as BROVANA, increase the risk of death in people with COPD.



Twice-Daily  
**Brovana**<sup>®</sup> 15 mcg  
(arformoterol tartrate) Inhalation Solution  
Get back into daily living

Notice of Violation

Patient Brochures

October 24, 2013



# Brovana<sup>®</sup> Product Labeling and Enforcement Example

**With the right COPD medicine, you may get back to daily living.**

- **One dose of BROVANA<sup>®</sup> (arformoterol tartrate) Inhalation Solution may help you breathe better for up to 12 hours at a time**
- **BROVANA is taken twice a day—once in the morning and once in the evening**
- **BROVANA is taken with a nebulizer, a device that turns BROVANA into a fine mist that's easy to breathe**
- **It takes just 5 to 10 minutes to take a dose of BROVANA**
- **BROVANA is covered under Medicare Part B\***

\*No guarantee of coverage.



Nebulizer system and BROVANA are sold separately.

Twice-Daily  
**Brovana<sup>®</sup> 15 mcg**  
(arformoterol tartrate) Inhalation Solution  
**Get back into daily living**





# Brovana<sup>®</sup> Product Labeling and Enforcement Example

- **Overstatement the Efficacy**
  - Claims suggest that an outcome of treatment with Brovana is the ability for patients to resume their baseline activities of daily living.
- **Clinical Studies**
  - BROVANA Inhalation Solution 15 mcg twice daily resulted in a statistically significant change of approximately 11% in mean forced expiratory volume in one second (FEV<sub>1</sub>) (as measured by percent change from study baseline FEV<sub>1</sub> at the end of the dosing interval over the 12 weeks of treatment, the primary efficacy endpoint) compared to placebo.



# **Brovana<sup>®</sup> Product Labeling and Enforcement Example**

## **Patient Brochures Claims:**

- **“If you have COPD, Are you using your nebulizer sometimes 4 or more times a day?”**
- **“If you have COPD, Do you feel you’re just not able to breathe in all your medicine?”**
- **“If you have COPD, Is it hard for you to depress your inhaler and time your breaths to get your medicine out?”**
- **“If you have COPD, Do you take your medicine correctly, but still feel like you may need something more?”**





# Brovana<sup>®</sup> Product Labeling and Enforcement Example

**Do any of the statements below capture how you feel? Check the ones that do.**

- I use my nebulizer sometimes 4 or more times a day—so it's often easier for me just to stay at home. Sometimes I even need it in the middle of the night
- When I use my inhaler, it just doesn't feel like I'm able to breathe in all of my medicine, or that all the medicine is coming out
- My hands don't move as well anymore, so it's hard for me to use my inhaler. I have trouble timing my hands with my breathing
- I'm taking my medicine, but it feels like I may need something more

**Bring this with you into the exam room,  
and ask your doctor if BROVANA<sup>®</sup> (arformoterol tartrate) Inhalation Solution  
is right for you.**



# Brovana<sup>®</sup> Product Labeling and Enforcement Example

## Unsubstantiated Superiority Claims

- Claims suggest that Brovana will be effective for those who have not had success with other COPD therapies based on Brovana's ability to overcome potential challenges associated with these therapies (e.g., therapies dosed  $\geq 4$  times/day or delivery system (e.g., DPIs or MDIs)).
- **Clinical Studies**
  - Trials included an active comparator (salmeterol). However, studies were not designed to measure clinical superiority.



# Brovana<sup>®</sup> Product Labeling and Enforcement Example

- **Unsubstantiated Claims**
  - Claims regarding the potential difficulty patients may encounter depressing an inhaler to administer therapy are misleading because they imply that patients with compromised manual dexterity will more easily be able to administer Brovana as compared to other COPD inhaler therapies.
  - Medication Guide includes lengthy directions for use.
  - In the absence of adequate evidence to demonstrate that patients with compromised manual dexterity are more easily able to administer Brovana as compared to other inhaled COPD therapies, the claims are misleading.





# Brovana<sup>®</sup> Product Labeling and Enforcement Example

- **Minimization of Risk**
  - Efficacy claims prominently presented in large, bolded font size and colorful text and graphics surrounded by a significant amount of white space
  - Risk information presented in small font, surrounded by little white space, and in single-spaced format

## INDICATION

BROVANA<sup>®</sup> (arformoterol tartrate) Inhalation Solution is a medicine called a long-acting beta<sub>2</sub>-agonist or LABA. BROVANA is used long term, twice a day (morning and evening), in controlling symptoms of chronic obstructive pulmonary disease (COPD) in adults with COPD. BROVANA is for inhalation use only through a standard jet nebulizer connected to an air compressor and should not be swallowed or injected.

## IMPORTANT PATIENT INFORMATION

**People with asthma who take long-acting beta<sub>2</sub>-adrenergic agonist (LABA) medicines such as BROVANA have an increased risk of death from asthma problems. It is not known if LABA medicines, such as BROVANA, increase the risk of death in people with COPD.**

BROVANA does not relieve sudden symptoms of COPD and should not be used more than twice a day. Always have a short-acting beta<sub>2</sub>-agonist with you to treat sudden symptoms.

Get emergency medical care if breathing problems worsen quickly or you use your short-acting beta<sub>2</sub>-agonist medicine but it does not relieve your breathing problems.

Do not stop using BROVANA unless told to do so by your healthcare provider because your symptoms might get worse.

When you are using BROVANA twice a day, do not use other medicines that contain a LABA for any reason.

BROVANA should not be used in children.

Tell your doctor if you have a heart condition or high blood pressure. Some people may experience increased blood pressure, heart rate or changes in heart rhythm.

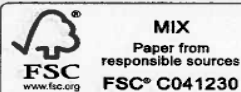
In COPD clinical trials, the five most common adverse events reported with BROVANA were pain, chest pain, back pain, diarrhea, and sinusitis. Other possible side effects include headache, tremor, nervousness, and dizziness.

Please see the accompanying full Prescribing Information and Medication Guide for BROVANA.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit [www.fda.gov/medwatch](http://www.fda.gov/medwatch) or call 1-800-FDA-1088.

The health information contained herein is provided for educational purposes only and is not intended to replace discussions with a healthcare provider.

All decisions regarding patient care must be made with a healthcare provider, considering the unique characteristics of the patient. BROVANA is a medicine used to treat COPD in adults. Remember that no medicine is right for everyone. Only your doctor can prescribe BROVANA for you.



BROVANA is a registered trademark of Sunovion Pharmaceuticals Inc.  
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All rights reserved. 10/12 BROV138-12



*Get back into daily living*



# Diclegis Product Labeling and Enforcement Example

- **Indication**

- For the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management

- **Limitations of Use**

- DICLEGIS has not been studied in women with hyperemesis gravidarum.





# Diclegis Product Labeling and Enforcement Example

- **Contraindications**

- Women known hypersensitivity to doxylamine succinate, other ethanolamine derivative antihistamines, pyridoxine hydrochloride or any inactive ingredient in the formulation, as well as in women who are taking monoamine oxidase inhibitors (MAOIs)

- **Warnings and Precautions**

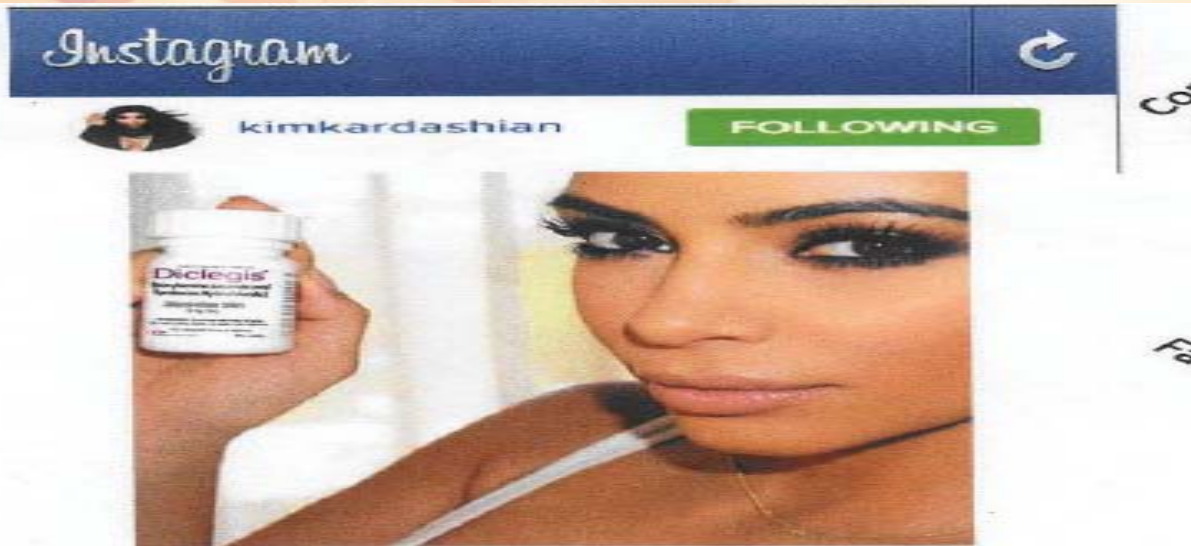
- Activities requiring mental alertness and concomitant medical conditions

- **Adverse reactions (most common)**

- Somnolence



# Diclegis Product Labeling and Enforcement Example



OMG. Have you heard about this? As you guys know my #morningsickness has been pretty bad. I tried changing things about my lifestyle, like my diet, but nothing helped, so I talked to my doctor. He prescribed me #Diclegis, and I felt a lot better and most importantly, it's been studied and there was no increased risk to the baby. I'm so excited and happy with my results that I'm partnering with Duchesnay USA to raise awareness about treating morning sickness. If you have morning sickness, be safe and sure to ask your doctor about the pill with the pregnant woman on it and find out more [www.diclegis.com](http://www.diclegis.com); [www.DiclegisImportantSafetyInfo.com](http://www.DiclegisImportantSafetyInfo.com)

## Warning Letter

Kim Kardashian  
Social Media Post

August 7, 2015



# Diclegis Product Labeling and Enforcement Example

- **Omission of Risk**

- Presents various efficacy claims for Diclegis. However, it entirely omits all risk information.
- Statements “[F]ind out more [www.diclegis.com](http://www.diclegis.com); [www.DiclegisImportantSafetyInfo.com](http://www.DiclegisImportantSafetyInfo.com)[,]” do not mitigate omission of risk.

- **Omission of Material Fact**

- Failed to provide material information that Diclegis has not been studied in women with hyperemesis gravidarum





# Diclegis Corrective

Instagram

Get the app Log in



kimkardashian

FOLLOW

413k likes

3w

kimkardashian #CorrectiveAd I guess you saw the attention my last #morningsickness post received. The FDA has told Duchesnay, Inc., that my last post about Diclegis (doxylamine succinate and pyridoxine HCl) was incomplete because it did not include any risk information or important limitations of use for Diclegis. A link to this information accompanied the post, but this didn't meet FDA requirements. So, I'm re-posting and sharing this important information about Diclegis. For US Residents Only.

Diclegis is a prescription medicine used to treat nausea and vomiting of pregnancy in women who have not improved with change in diet or other non-medicine treatments.

Limitation of Use: Diclegis has not been studied in women with hyperemesis gravidarum.

Log in to like or comment.







# Clinical Outcome Assessment (COA) Promotional Claims

**COA:** any assessment that may be influenced by human choices, judgment, or motivation and may either support direct or indirect evidence of treatment benefit.

- **Patient-reported outcomes (PROs)**
- **Clinician-reported outcomes (ClinROs)**
- **Observer-reported outcomes (ObsROs)**
- **Performance outcomes (PerfOs)**



# Clinical Outcome Assessment (COA) Promotional Claims

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## **Guidance for Industry** **Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims**

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)

December 2009  
Clinical/Medical

---

- Serves as the “gold standard” for good measurement principles for any COA
- Outlines how the FDA interprets “well-defined and reliable” measures intended to provide evidence of treatment benefit



# Clinical Outcome Assessment (COA) Promotional Claims

## General Considerations with COAs:

- In general, the **same** study principles that apply to other clinical endpoint measures apply to reported assessments (PROs, ClinROs, and ObsROs).
  - Should be designated as **primary** or **key secondary** endpoints
- Instruments for reported assessments need to be **well-defined** and **reliable** in the clinical trial context of use.
  - **Content validity** of instruments need to be established



# Clinical Outcome Assessment (COA) Promotional Claims

Labeling Example:

Approved Product  
Labeling for  
Jakafi™

(ruxolitinib), tablets  
for oral use

November 2011

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use JAKAFI safely and effectively. See [full prescribing information](#) for JAKAFI.

JAKAFI™ (ruxolitinib) tablets, for oral use  
Initial U.S. Approval: 2011

## INDICATIONS AND USAGE

Jakafi is a kinase inhibitor indicated for treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis. (1)

## DOSAGE AND ADMINISTRATION

- The starting dose of Jakafi is 20 mg given orally twice daily for patients with a platelet count greater than  $200 \times 10^9/L$ , and 15 mg twice daily for patients with a platelet count between  $100 \times 10^9/L$  and  $200 \times 10^9/L$ . (2.1)
- Perform a complete blood count before initiating therapy with Jakafi. Monitor complete blood counts every 2 to 4 weeks until doses are stabilized, and then as clinically indicated. Modify dose for thrombocytopenia. (2.1) (2.2)
- Increase dose based on response and as recommended to a maximum of 25 mg twice daily. Discontinue after 6 months if no spleen reduction or symptom improvement (2.3)

## DOSAGE FORMS AND STRENGTHS

Tablets: 5 mg, 10 mg, 15 mg, 20 mg and 25 mg. (3)

## CONTRAINDICATIONS

None. (4)

## WARNINGS AND PRECAUTIONS

- Thrombocytopenia, anemia and neutropenia can occur. Manage by dose reduction, or interruption or transfusion. (5.1)





# Clinical Outcome Assessment (COA) Promotional Claims

## Jakafi™ Labeling Example:

### Clinical Studies:

- The primary efficacy endpoint was the proportion of pts achieving  $\geq 35\%$  reduction from baseline in spleen volume at Week 24 (measured by MRI or CT).
- A key secondary endpoint was the proportion of pts with a  $>50\%$  reduction in Total Symptom Score from baseline to Week 24, as measured by the modified Myelofibrosis Symptom Assessment Form (MFSAF) v2.0 diary.



# Clinical Outcome Assessment (COA) Promotional Claims

## Jakafi™ Labeling Example:

### Instrument:

- The MFSAF is a daily diary that captures the core symptoms of myelofibrosis (abdominal discomfort, pain under left ribs, night sweats, itching, bone/muscle pain, and early satiety).
- Symptom scores range from 0 (no symptoms) to 10 (“worst imaginable” symptoms). The scores were added to create the daily total score (maximum=60).



# Clinical Outcome Assessment (COA) Promotional Claims

## Jakafi™ Labeling Example:

### Results:

- A higher proportion of pts in the Jakafi group had a 50% or greater reduction in Total Symptom Score than in the placebo group, with a median time to response of <4 weeks.

**Table 7: Improvement in Total Symptom Score**

	Jakafi (N=148)	Placebo (N=152)
Number (%) of Patients with 50% or Greater Reduction in Total Symptom Score by Week 24	68 (45.9)	8 (5.3)
P-value	< 0.0001	

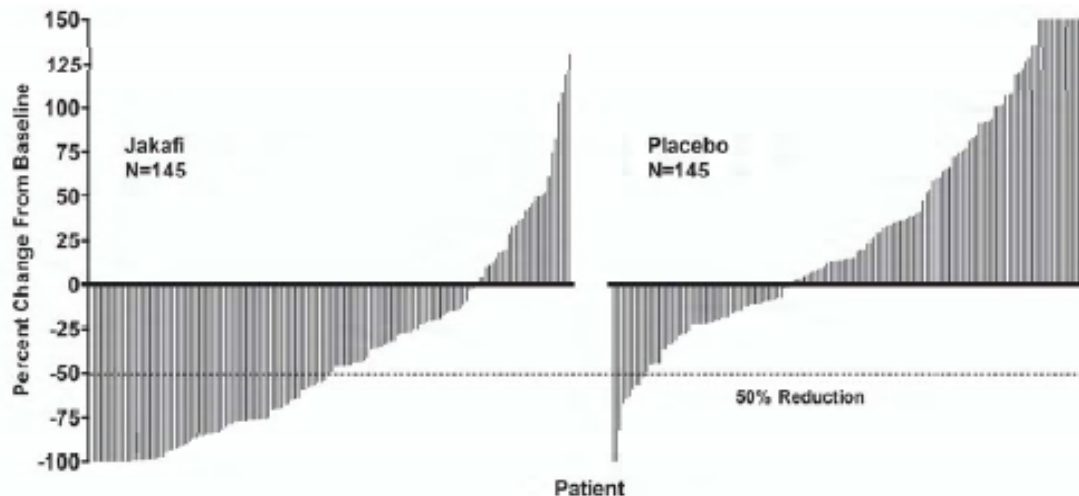


# Clinical Outcome Assessment (COA) Promotional Claims

## Jakafi™ Labeling Example:

Figure 2 shows the percent change from baseline in Total Symptom Score for each patient at Week 24 (Jakafi N=129, placebo N=103) or the last evaluation on randomized therapy prior to Week 24 for patients who did not complete 24 weeks of randomized treatment (Jakafi N=16, placebo N=42). Results are excluded for 5 patients with a baseline Total Symptom Score of zero, 8 patients with missing baseline and 6 patients with insufficient post-baseline data.

**Figure 2: Percent Change from Baseline in Total Symptom Score at Week 24 or Last Observation for Each Patient (Study 1)**



Worsening of Total Symptom Score is truncated at 150%.

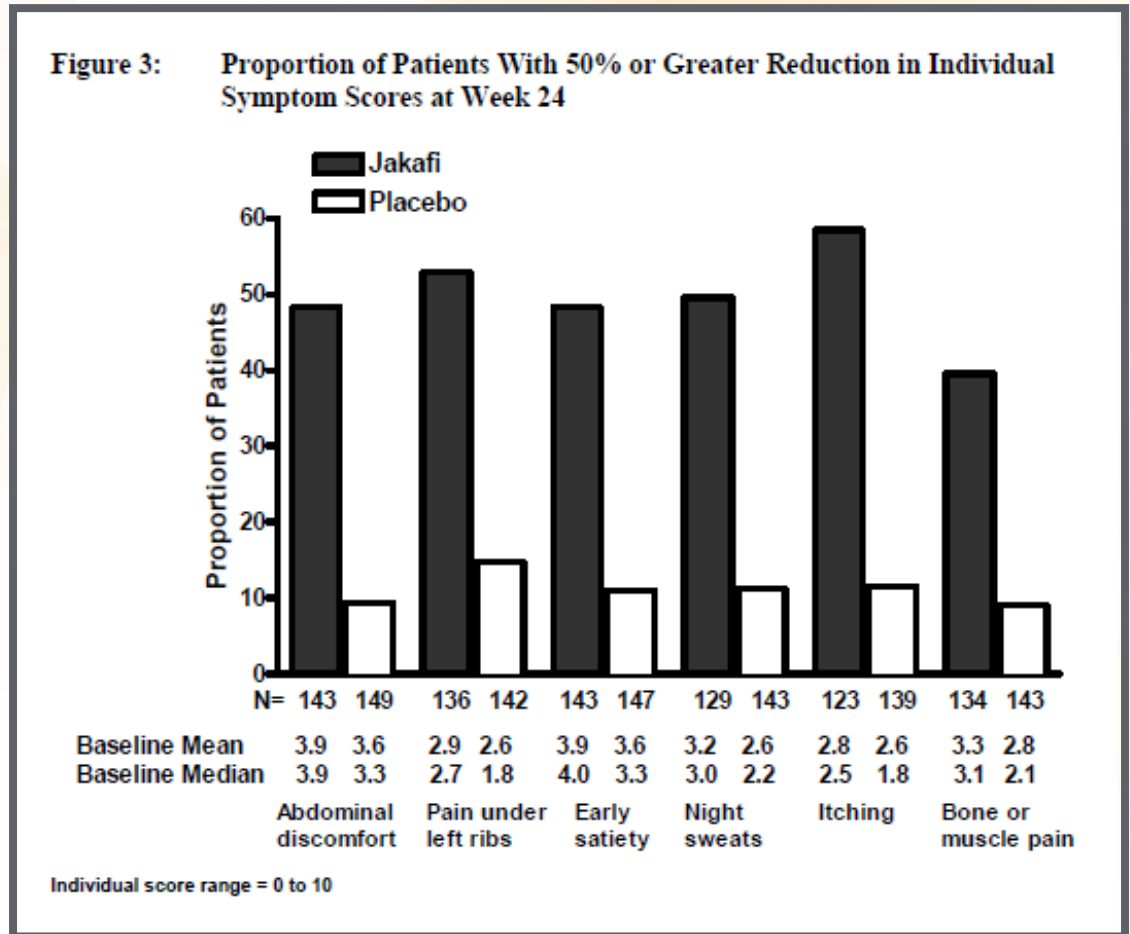




# Clinical Outcome Assessment (COA) Promotional Claims

## Jakafi™ Labeling Example:

This figure indicates that all 6 of the symptoms contributed to the higher Total Symptom Score response rate in the Jakafi group.



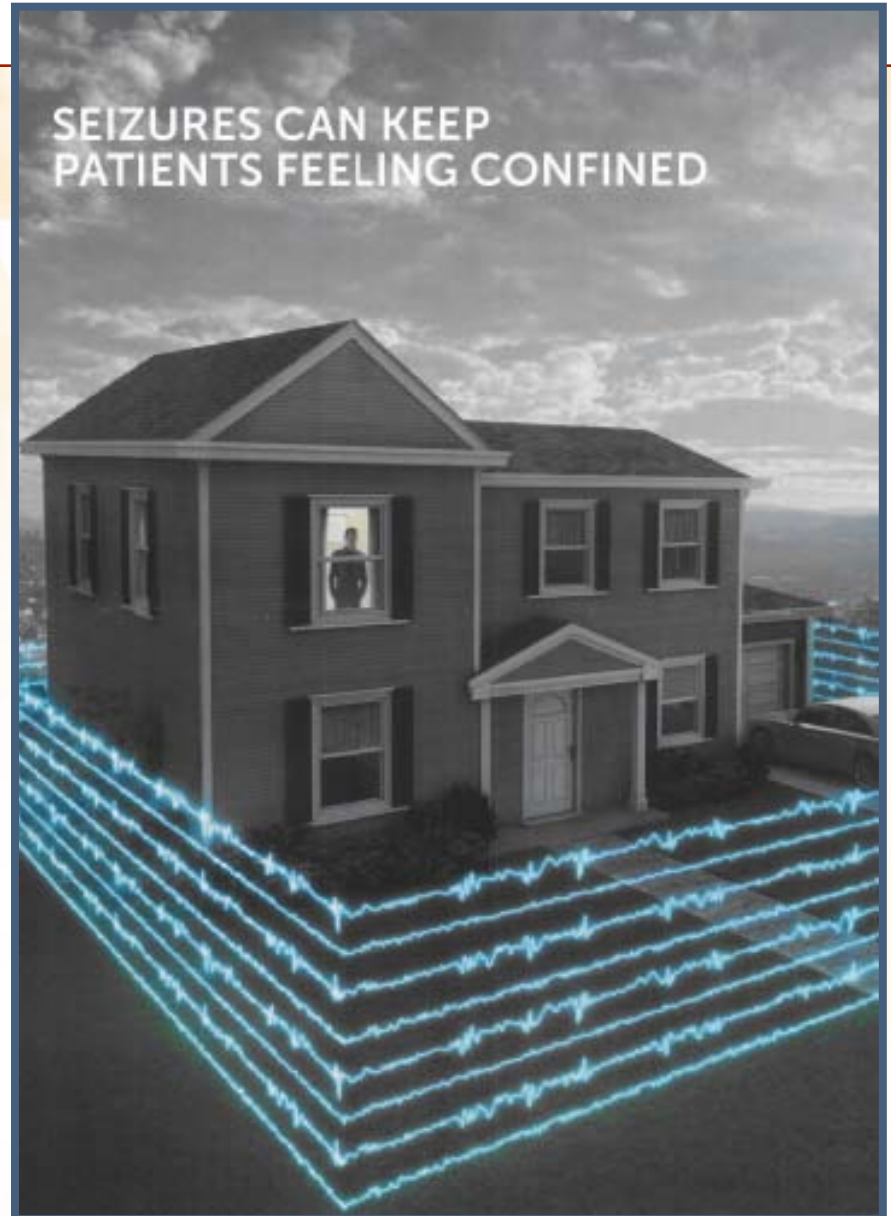


# Enforcement Examples with COA Claims

## Notice of Violation:

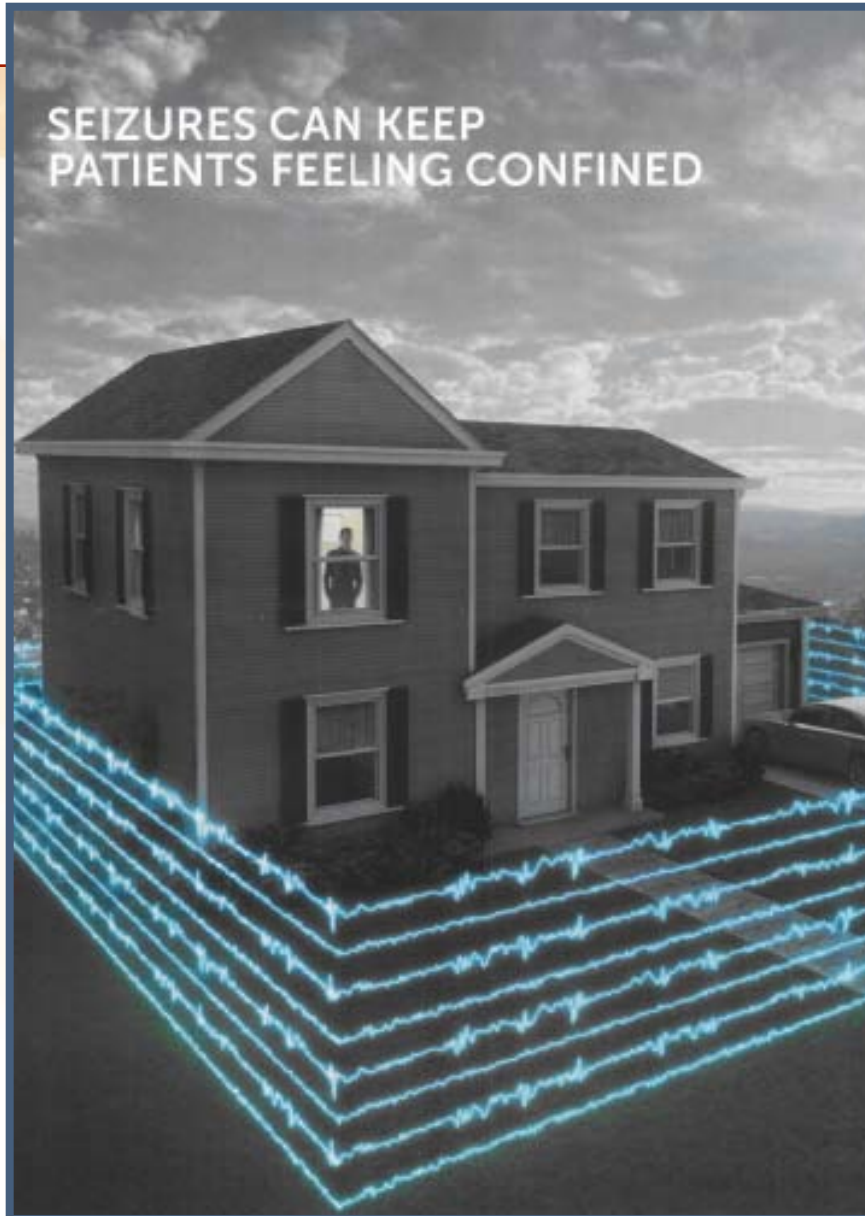
**Aptiom®**  
(eslicarbazepine acetate) Tablets

December 15, 2014





# Enforcement Examples with COA Claims







# Enforcement Examples with COA Claims

For the adjunctive treatment of partial-onset seizures  
**PUT PATIENTS ON A PATH TO  
POWERFUL SEIZURE REDUCTION**

Learn more about APTIOM  
at AES Booth 105

## Reduce seizure frequency with once-daily Aptiom® (eslicarbazepine acetate)

- Significant reduction in seizure frequency in 3 randomized, double-blind, placebo-controlled studies\*\*
- Incidences of aggression and agitation comparable to placebo†
- In most patients, titration is 1 step, 1 week to the recommended maintenance dose! –May be taken either whole or crushed, with or without food‡

### Indication and Usage

APTIOM is indicated as adjunctive treatment of partial-onset seizures.

### Important Safety Information for APTIOM

- **Contraindications:** APTIOM is contraindicated in patients with a hypersensitivity to eslicarbazepine acetate or oxcarbazepine.
- **Suicidal Behavior and Ideation:** Antiepileptic drugs (AEDs), including APTIOM, increase the risk of suicidal thoughts or behavior. Anyone considering prescribing APTIOM or any other AED must balance this risk with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. Patients and caregivers should also be advised to be alert to these behavioral changes and to immediately report them to the healthcare provider.
- **Serious Dermatologic Reactions,** including Stevens-Johnson Syndrome (SJS) have been reported in association with APTIOM use. Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and SJS, have been reported in patients using oxcarbazepine or carbamazepine, which are chemically related to APTIOM. Should a patient develop a dermatologic reaction while using APTIOM, discontinue APTIOM use unless it is clearly not drug related.
- **Adverse Reactions:** The most frequently reported adverse reactions in patients receiving APTIOM at doses of 800 mg or 1200 mg (≥4% and ≥2% greater than placebo) were dizziness, somnolence, nausea, headache, diplopia, vomiting, fatigue, vertigo, ataxia, blurred vision, and tremor.
- **Study design:** Three studies, each consisting of 8-week baseline, 2-week titration, and 12-week maintenance phases, established the efficacy of APTIOM in patients with partial-onset seizures not adequately controlled with 1–3 AEDs. The standardized seizure frequency during the maintenance phase over 28 days was the primary endpoint. APTIOM 400 mg/day was evaluated in Studies 1 and 2 and did not show significant treatment effect. Treatment effects were statistically significant with APTIOM 800 mg/day in Studies 1 and 2, but not in Study 3, and with APTIOM 1200 mg in all 3 studies.†

Please see additional  
Important Safety Information  
and Brief Summary of Prescribing  
Information on adjacent pages.

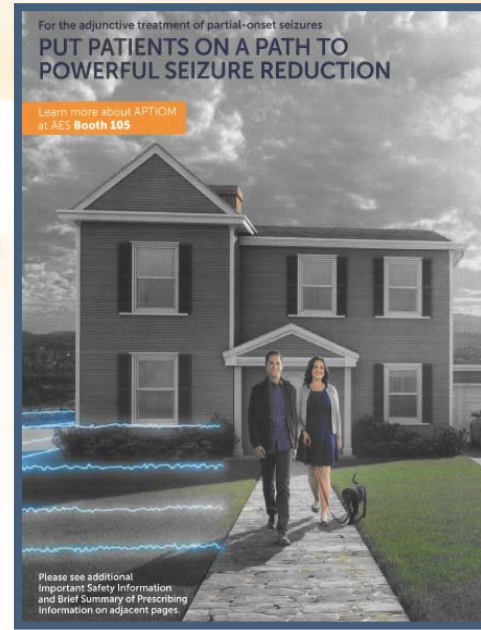
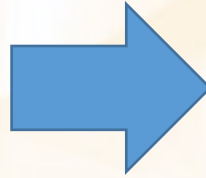
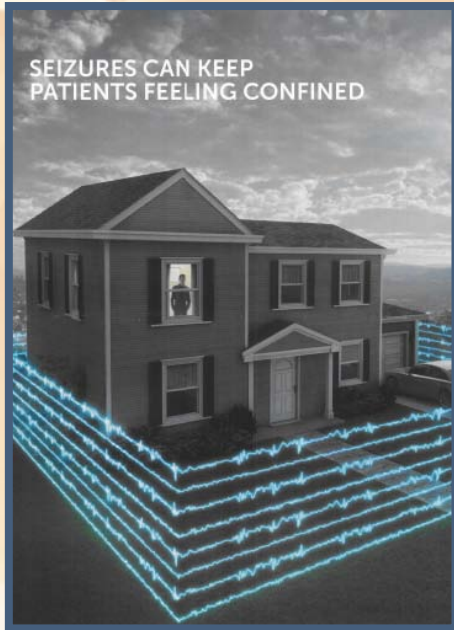
Learn more at  
[www.AptiomHCP.com/info](http://www.AptiomHCP.com/info)

ONCE DAILY  
**Aptiom**  
(eslicarbazepine acetate) tablets  
200 mg • 400 mg • 600 mg • 800 mg





# Enforcement Examples with COA Claims



“The claims and presentations misleadingly overstate the efficacy of Aptiom by suggesting that the drug has been shown to have treatment benefits on patients’ feelings of confinement associated with seizures.”



# Enforcement Examples with COA Claims

## Aptiom Labeling (Sec 14 CLINICAL STUDIES):

**Table 4: Standardized Seizure Frequency During the Maintenance Phase Over 28 Days and Percent Reduction from Baseline in Seizure Frequency**

	Placebo	APTIOM	
		800 mg	1200 mg
<b>Study 3</b>			
N	95	88	87
Seizure Frequency (LS Mean seizures per 28 days) (p-value)	6.6	5.0 (0.047 <sup>*</sup> )	4.3 (0.001 <sup>*</sup> )
Median Percent Reduction from Baseline in Seizure Frequency (%)	-15	-36	-39
<b>Study 4</b>			
N	99	87	81
Seizure Frequency (LS Mean seizures per 28 days) (p-value)	8.6	6.2 (0.006 <sup>*</sup> )	6.6 (0.042 <sup>*</sup> )
Median Percent Reduction from Baseline in Seizure Frequency (%)	-6	-33	-28
<b>Study 5</b>			
N	212	200	184
Seizure Frequency (LS Mean seizures per 28 days) (p-value)	7.9	6.5 (0.058)	6.0 (0.004 <sup>*</sup> )
Median Percent Reduction from Baseline in Seizure Frequency (%)	-22	-30	-36

\*statistically significant compared to placebo



# Enforcement Examples with COA Claims

## Aptiom Labeling (Sec 14 CLINICAL STUDIES):

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# Enforcement Examples with COA Claims

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Seizure Frequency (LS Mean seizures per 28 days) (p-value)	7.9	6.5 (0.058)	6.0 (0.004*)
Median Percent Reduction from Baseline in Seizure Frequency (%)	-22	-30	-36

\*statistically significant compared to placebo

- “Although Aptiom may reduce seizure frequency, FDA is not aware of substantial evidence demonstrating any effectiveness of Aptiom on patients’ feelings on confinement associated with seizures.”
- No patient-reported data in the labeling





# Enforcement Examples with COA Claims

Notice of Violation:

Rapaflo® (silodosin)  
Capsule for oral use

May 19, 2015

**RAPAFLO<sup>®</sup>**  
(silodosin) capsules  
TAKE CONTROL OF YOUR BPH

SEARCH

EMAIL A COLLEAGUE | PRESCRIBING INFORMATION | CONSUMER SITE

HOME | ABOUT BPH | ABOUT RAPAFLO<sup>®</sup> | RESOURCE CENTER | RAPAFLO<sup>®</sup> CLINICAL DATA

**BPH SYMPTOM RELIEF THAT WORKS NIGHTS SO HE CAN WORK DAYS**

**WELCOME TO THE RAPAFLO<sup>®</sup> PROFESSIONAL SITE**

RAPAFLO<sup>®</sup> is a uniquely selective alpha-blocker that provides rapid and sustained relief of benign prostatic hyperplasia (BPH) symptoms with a low incidence of vasodilatory and orthostatic effects.<sup>1,2</sup> RAPAFLO<sup>®</sup> has been proven safe and effective for the treatment of frequency, nocturia, and other bothersome BPH symptoms in multiple patient types.<sup>2,3</sup>

**AN ONLINE RESOURCE FOR HEALTH CARE PROFESSIONALS TO LEARN ABOUT:**

<a href="#">The safety, efficacy, and mechanism of action of RAPAFLO<sup>®</sup></a>	<a href="#">How to start a conversation about BPH with your older male patients</a>	<a href="#">BPH and its impact</a>
<a href="#">RAPAFLO<sup>®</sup> dosing and administration</a>	<a href="#">How to assess the severity of your patients' BPH symptoms and make a diagnosis</a>	<a href="#">Appropriate treatment options for BPH</a>
<a href="#">RAPAFLO<sup>®</sup> access and reimbursement</a>		<a href="#">Professional resources for you and your patients</a>

**+ REFERENCES**

RAPAFLO<sup>®</sup> is indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH). RAPAFLO<sup>®</sup> is not indicated for the treatment of hypertension.

**IMPORTANT SAFETY INFORMATION**

RAPAFLO<sup>®</sup> is contraindicated in patients with severe renal impairment (Cr<30 mL/min), severe hepatic impairment (Child-Pugh score >10), with use of strong CYP3A4 inhibitors, and in patients with a history of hypersensitivity to silodosin or any of the ingredients of RAPAFLO<sup>®</sup>.

Postural hypotension with or without symptoms (eg, dizziness) may develop when beginning treatment with RAPAFLO<sup>®</sup>. As with all alpha-blockers, there is a potential for syncope. Patients should be warned of the possible occurrences of such events and should avoid situations where injury could result. RAPAFLO<sup>®</sup> should be used with caution in patients with moderate renal impairment. Patients should be assessed to rule out the presence of prostate cancer prior to starting treatment with RAPAFLO<sup>®</sup>. Patients planning cataract surgery should inform their ophthalmologist that they are taking RAPAFLO<sup>®</sup>.

The most common side effects are retrograde ejaculation, dizziness, diarrhea, orthostatic hypotension, headache, nasopharyngitis, and nasal congestion.

**Actavis**

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LEGAL/COPYRIGHT | DISCLAIMER | PRIVACY POLICY | 0608 | 6/13



# Enforcement Examples with COA Claims

The screenshot displays the Rapaflo website interface. At the top left is the Rapaflo logo, which includes the text "Rapaflo<sup>®</sup> (silodosin) capsules" and the tagline "TIGHT CONTROL OF YOUR BPH". To the right of the logo is a search bar with the word "SEARCH" and a magnifying glass icon. Below the search bar are three links: "EMAIL A COLLEAGUE", "PRESCRIBING INFORMATION", and "CONSUMER SITE". A blue navigation bar contains five menu items: "HOME", "ABOUT BPH", "ABOUT RAPAFLO", "RESOURCES CENTER", and "RAPAFLO CLINICAL DATA". The main content area features a large banner with a photograph of a man in a white shirt standing in a doorway, looking towards a woman who is lying in bed. The text on the banner reads: "BPH SYMPTOM RELIEF THAT WORKS NIGHTS SO HE CAN WORK DAYS".



# Enforcement Examples with COA Claims

The presentation is misleading because it “implies that in addition to improving BPH symptoms, Rapaflo has also been shown to improve both sleep disturbance (i.e., quality of sleep) and work productivity.”



# Enforcement Examples with COA Claims

## Rapaflo Labeling (Sec 14 CLINICAL STUDIES):

### 14.1 Benign Prostatic Hyperplasia

Two 12-week, randomized, double-blind, placebo-controlled, multicenter studies were conducted with 8 mg daily of silodosin. In these two studies, 923 patients [mean age 64.6 years; Caucasian (89.3%), Hispanic (4.9%), Black (3.9%), Asian (1.2%), Other (0.8%)] were randomized and 466 patients received RAPAFLO 8 mg daily. The two studies were identical in design except for the inclusion of pharmacokinetic sampling in Study 1. The primary efficacy assessment was the International Prostate Symptom Score (IPSS) which evaluated irritative (frequency, urgency, and nocturia), and obstructive (hesitancy, incomplete emptying, intermittency, and weak stream) symptoms. Maximum urine flow rate (Q<sub>max</sub>) was a secondary efficacy measure.





# Enforcement Examples with COA Claims

## Rapaflo Labeling (Sec 14 CLINICAL STUDIES):

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Two 12-week, randomized, double-blind, placebo-controlled, multicenter studies were conducted with 8 mg daily of silodosin. In these two studies, 923 patients [mean age 64.6 years; Caucasian (89.3%), Hispanic (4.9%), Black (3.9%), Asian (1.2%), Other (0.8%)] were randomized and 466 patients received RAPAFLO 8 mg daily. The two studies were identical in design except for the inclusion of pharmacokinetic sampling in Study 1. The primary efficacy assessment was the International Prostate Symptom Score (IPSS) which evaluated irritative (frequency, urgency, and nocturia), and obstructive (hesitancy, incomplete emptying, intermittency, and weak stream) symptoms. Maximum urine flow rate (Q<sub>max</sub>) was a secondary efficacy measure.



# Enforcement Examples with COA Claims

## Rapaflo Labeling (Sec 14 CLINICAL STUDIES):

in design except for the inclusion of pharmacokinetic sampling in Study 1. The primary efficacy assessment was the International Prostate Symptom Score (IPSS) which evaluated irritative (frequency, urgency, and nocturia), and obstructive (hesitancy, incomplete emptying, intermittency, and weak stream) symptoms. Maximum urine flow rate (Qmax) was a secondary efficacy measure.

- “These studies did not measure the impact of treatment on individual symptoms, such as nocturia. Therefore, efficacy claims and presentations for Rapaflo that suggest improvement in one of the IPSS subscore symptoms (i.e., nocturia) are not supported by substantial evidence.”
- “Moreover, the pivotal studies did not evaluate the impact of Rapaflo on quality of sleep or work productivity.”



# Enforcement Examples with COA Claims

## Warning Letter:

**Luvox CR®**

(fluvoxamine maleate)

Extended-Release  
Capsules

July 6, 2010

*Blushing*

*Avoiding  eye contact*

*What do social situations  
bring out in you?*


*Sweating*

*Tremors*



# Enforcement Examples with COA Claims

The patient brochure includes a patient profile for Ana, a 19-year-old college student.



**Ana, 19\***  
College student

**How it started**

I think I was a pretty typical high school student. I went to school every morning, joined a few clubs after school, and started flute lessons. I guess I was always a bit shy but no more than anyone else, really. But during my junior year, something changed. I still did all my work, but anything after school? Well, that wasn't for me anymore. I'd go home right away. I'd stay in my room, watch TV, do nothing. Then I did less.

I started to skip lunch because I couldn't bear the thought of eating in front of others. At different times of the day, I'd have really bad stomachaches, sweat through my shirt, or feel my heart just going crazy in my chest.

I thought maybe I'm just "down." I even went to see the guidance counselor at school. She told me the same thing, "Don't worry, Ana, everyone feels down sometimes." She smiled, "even me."

I left and went back home. And pulled down the blinds.

\*Not an actual patient.





# Enforcement Examples with COA Claims

## **Trapped**

I graduated and went off to college. Now I felt anxious all the time. It was just a fog that surrounded my life. A knot in my stomach that I could never untie. It hung over my head. Every morning, normal life happened around me, but every morning, I was stuck in my room, losing day after day after day.

The knots would form in my stomach weeks ahead of anything social. If I was invited to a birthday party, my palms would get sweaty and my heart would race. I'd look in a mirror and my face would be beet red. Hot to the touch. It didn't make any sense. I wanted to go to these parties and make friends like everyone else. But as much as I tried, I just couldn't bring myself to get past the door.

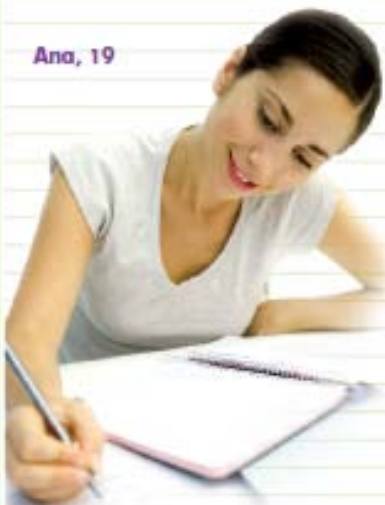
So I made excuses as to why I couldn't go out. I'd sit alone in my dorm room feeling nervous and sick to my stomach. I stopped going to class. My grades were suffering. If I kept it up, I would flunk out of school.

I knew other people who were anxious. They went to see a psychiatrist and took medication. I was sure that if I were strong enough, I could get through these feelings on my own. But nothing worked. I felt like I was losing my mind. It was like I was trapped in a nightmare that I had no way of getting out of.

“The knots would form in my stomach weeks ahead of anything social...So I made excuses as to why I couldn't go out. I'd sit alone in my dorm room feeling nervous and sick to my stomach. I stopped going to class. My grades were suffering. If it kept up, I would flunk out of school. I knew other people who were anxious. They went to see a psychiatrist and took medication.”



# Enforcement Examples with COA Claims



**Ana, 19**

**EMPOWER PLAY. Luvox CR**  
Luvox CR is a prescription medicine used to treat SAD.

### Why did I get treated for SAD?

I know other people who maybe have the same symptoms but just accept them. I guess I realized I just wasn't going to be one of them. Having SAD doesn't mean I have to live with it.

All patients are different and individuals respond differently to both medications and therapy. Like I did with my doctor, you and your doctor will determine a treatment plan for you.

I believe...  
some...  
treat...  
to the...  
asked...  
was a...  
I think...  
My psy...  
over tim...  
I'm just

### The help that I needed

Once I started seeing my psychiatrist, he helped me manage my SAD, and I've been doing a lot better. It's not over yet. I have a long way to go. But seeing progress like this really encourages me to keep up my treatment.

Recently, I got a B on my bio midterm and I've been playing flute in a jazz quartet after classes. Small steps, but everything is starting to go well. My psychiatrist is really pleased and thinks I'm doing better.

He reminded me that before I accepted I had SAD, I wasn't like this. But sticking with my treatment and taking my Luvox CR has really helped me. I don't feel trapped by SAD anymore.

For more...  
treat SA...

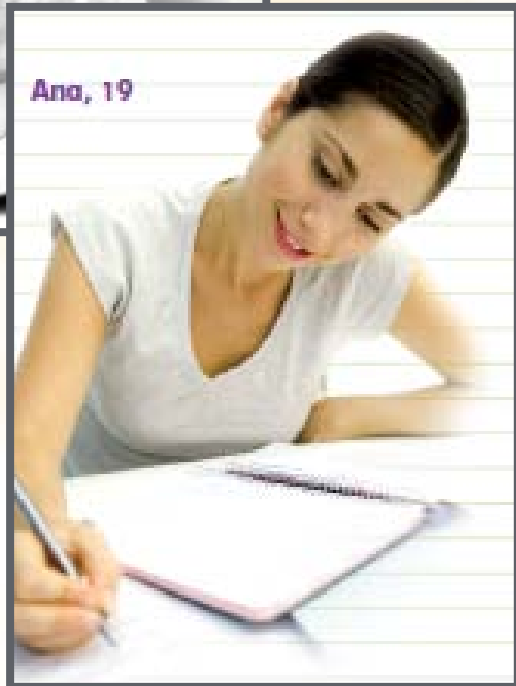
Please see accompanying full prescribing information, including boxed warning.

...ld form in my stomach  
... So I  
... is to why  
... in my dorm room  
... and sick in my

“Recently, I got a B on my bio midterm and I’ve been playing flute in a jazz quartet after classes. Small steps, but everything is starting to go well. My psychiatrist is really pleased and thinks I’m doing better.”



# Enforcement Examples with COA Claims



“The overall impression created by these presentations is that the treatment with Luvox CR will markedly improve a patient’s social functioning and academic performance...We are not aware of substantial evidence or substantial clinical experience to support the implication that patients treated with Luvox CR will experience such improvements in social functioning or academic performance.”



# Enforcement Examples with COA Claims

## Luvox CR Labeling (CLINICAL PHARMACOLOGY):

### Clinical Trials

*Social Anxiety Disorder:* The effectiveness of LUVOX CR Capsules in the treatment of social anxiety disorder was demonstrated in two 12-week, multicenter, placebo-controlled studies of adult outpatients with social anxiety disorder (DSM-IV). Patients in these trials were titrated in 50 mg increments over the first six weeks of the study on the basis of response and tolerance from a dose of 100 mg/day to a fluvoxamine maleate dose within a range of 100 mg to 300 mg once-a-day.

In these studies, the effectiveness of LUVOX CR Capsules compared to placebo was evaluated on the basis of change from baseline in the Liebowitz Social Anxiety Scale (LSAS). LUVOX CR Capsules demonstrated statistically significant superiority over placebo at the primary endpoint (Week 12) as assessed by the LSAS total score in both studies.





# Enforcement Examples with COA Claims

## Luvox CR Labeling (CLINICAL PHARMACOLOGY):

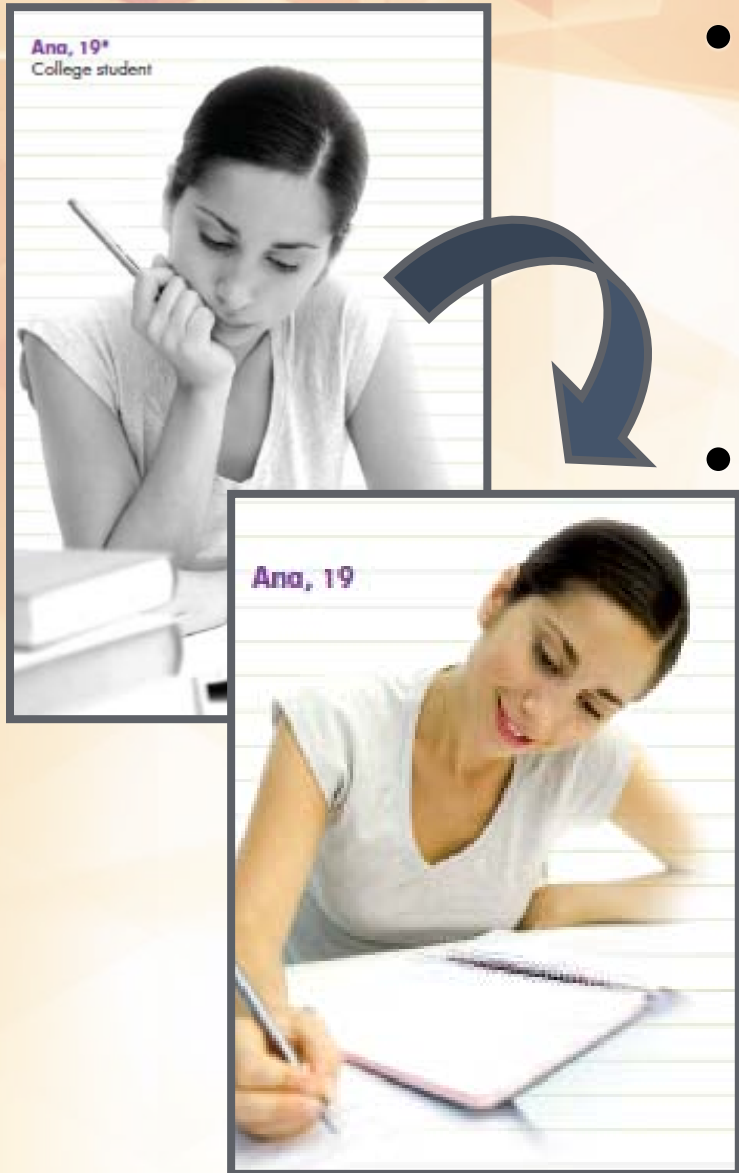
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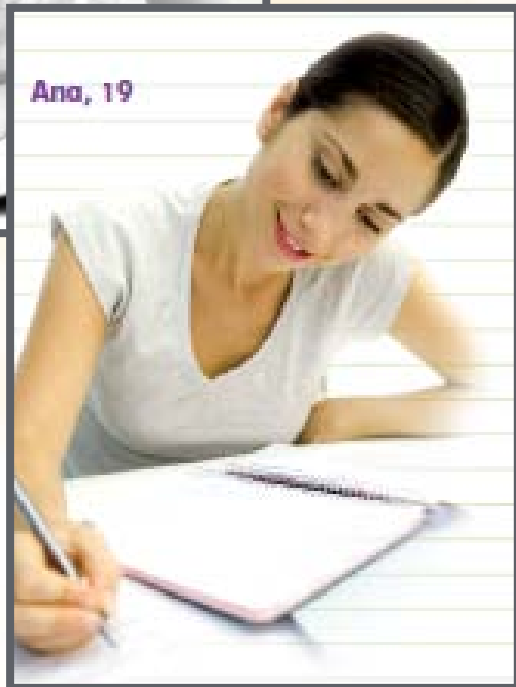
# Enforcement Examples with COA Claims



- Luvox CR has been shown to improve **total** scores in the Liebowitz Social Anxiety Scale (LSAS) at Week 12.
- The LSAS includes 6 subscales and 24 items:
  - Subscales include: total fear, fear of social interaction, fear of performance, total avoidance, avoidance of social interaction, and avoidance of performance



# Enforcement Examples with COA Claims



- The LSAS does not measure the impact of treatment on the 6 **individual** subscales or the 24 **individual** items.
- Clinical trial results showed improvements of **13.4** and **8.4** in total LSAS scores:
  - Scoring scale is in 15-point increments (moderate [55-65], marked [65-80], severe [80-95], very severe [>95])
  - No evidence that these improvements in LSAS scores correlate with the drastic improvements claimed



# Recommendations

- **Early** and proactive discussions with the appropriate review division on how best to plan for the interpretation of study findings to avoid conducting studies that are not able to support your desired labeling/promotional claims
  - Review divisions will consult with the COA Staff and/or OPDP as necessary.
  - Target Product Profile





# Conclusions

- **Labeling has a significant impact on drug promotion.**
- **Early communications with FDA is the key to optimizing your goals!**



# OPDP Contact Information

## **Telephone Number:**

301-796-1200

## **Fax Numbers:**

301-847-8444

301-847-8445

## **Submission Address:**

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion  
5901-B Ammendale Road  
Beltsville, MD 20705-1266



# OPDP Web Resources

- **OPDP home page**

<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm090142.htm>

- **OPDP organization listing**

<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm154886.htm>

- **Guidances**

<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm109905.htm#Guidances>

- **Warning and untitled letters**

[www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/default.htm](http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/default.htm)