Regulation of Prescription Drug Promotion

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Overview

- Office of Prescription Drug Promotion (OPDP)
  - Who We Are
  - What We Do
  - What We Regulate
- Regulatory authority
- Advertising and promotion
- Operational role
OPDP’s Mission

• To protect the public health by assuring prescription drug information is truthful, balanced and accurately communicated.

• To guard against false and misleading advertising and promotion through comprehensive surveillance, enforcement, and educational programs.
CDER → OMP → OPDP
What Does OPDP Regulate?

• Written and printed prescription drug promotional materials made by the company which include:
  • TV and radio commercials
  • Sales aids, journal ads, and patient brochures
  • Drug websites, e-details, webinars, Epocrates, and email alerts
DTC Myths and Misperceptions

• FDA “legalized” DTC advertising in the late 1990’s
• Industry spends most of its advertising budget on DTC advertising
• FDA has the authority to ban DTC advertising
• FDA can restrict DTC advertising to certain types of products
• FDA approves DTC ads
• FDA regulates “good taste”
Federal Food, Drug and Cosmetic Act (FFD&C Act)

• Code of Federal Regulations (CFR)
  – 202.1 - Prescription Drug Advertising
  – 312.7 - Preapproval Promotion
  – 314.550 - Subpart H, Accelerated Approval
  – 601.40 - Subpart E, Accelerated Approval for Biologics
Regulatory Authority

Post-Approval Regulations located in 21 CFR 314.81(b)(3):

– Require the submission of all promotional materials at the time of initial dissemination or publication
– Must include Form FDA 2253 and current PI
– OPDP receives >80K submissions per year
– OPDP does not generally “pre-clear” promotional materials
Categories of Promotional Materials
# Categories of Promotional Materials

<table>
<thead>
<tr>
<th>Accompanied By</th>
<th>Dissemination</th>
<th>Examples of Types of Materials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advertisements</strong></td>
<td>Brief Summary</td>
<td>Magazines, journals, periodicals, newspapers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Broadcast: TV, radio and telephone communication systems</td>
</tr>
<tr>
<td><strong>Promotional Labeling</strong></td>
<td>Product Labeling (PI)</td>
<td>Supplied by manufacturer, distributor, packer or any party acting on the sponsor’s behalf</td>
</tr>
</tbody>
</table>
Categories of Promotional Materials

Institutional Ad

Includes information such as
- Company name
- Area of Research

May not mention any drug names
Categories of Promotional Materials

Help Seeking/Disease Awareness Communications

May:
- Discuss a medical condition or disease state
- Include company name
- Not include drug name
Categories of Promotional Materials

Reminder Ad
1) Includes proprietary & established name
2) May call attention to drug name but may NOT contain any representation or suggestion relating to the advertised drug
3) May include dosage form, package contents, price, name of manufacturer, packer or distributor
4) Not permitted for drugs with a boxed warning
Categories of Promotional Materials

**Full Product Ad**
- Include representation or suggestion relating to the advertised drug product
- Must include a balanced risk presentation (‘‘fair balance’’)
- Must include the Brief Summary or PI

**Brief Summary**
Categories of Promotional Materials: DTC Broadcast Ad Nuances

• “Major Statement”
  – Information relating to the major side effects and contraindications

• “Adequate Provision”
  – Recognizes the inability of broadcast advertisements of reasonable length to present and communicate this information effectively
  – Provides for dissemination of the full prescribing information for the drug
    • Toll-free phone number
    • Simultaneously running magazine ad
    • Reference to healthcare provider
    • Website
What does OPDP do?

- Advice to industry
- Advice within FDA
- Guidances and Policy Development
- Research
- Surveillance and Enforcement
Advice to Industry

• Provide comments on DRAFT promotional materials (VOLUNTARY in most cases)
  • Launch materials for new drugs or new indications
  • Direct-to-consumer (DTC) broadcast ads
  • Non-launch materials

• Pre-submission required for certain drugs
  • (e.g., Subpart H/Subpart E “accelerated approval”)
Language in Approval Letters

PROMOTIONAL MATERIALS
You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

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

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm
Language in Approval Letters (Accelerated Approval)

PROMOTIONAL MATERIALS
Under 21 CFR 314.550, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 314.550, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved package insert (PI)/Medication Guide/patient PI (as applicable).
Launch Advisories

• First 120 days of marketing to public
• Prior to first use in public domain
  – Should not disseminate same/similar claims while review is pending
• Applies to new drug, indication, delivery system, formulation, or route of administration
• Certain types of materials
  • e.g., press releases, TV ads, sales aids, patient brochures, print ads, websites
  • Size limits
    – Sales aids/patient brochures/websites: 12 pages
    – Print ads: 4 pages
• Goal timeline: 45 calendar days (minus time required for medical officer consult)
Submitting Materials for Advisory Comments

• Claims or presentations **not in the public domain**
• Can bundle together into one submission (exception is TV ads)
  – Consolidate into single submission rather than sending the materials piecemeal in several submissions over the course of a few days/weeks.
  – submit professional and consumer materials separately
  – Separate launch core vs. launch non-core vs. non-launch
• If submitting professional and DTC core launch materials around same time, submit both on same day (same 45-day goal)
• Submit materials in hardcopy in triplicate unless otherwise specified
  – TV ads: 17 copies if first time on TV; 10 copies otherwise
• Do NOT include Form FDA-2253 or 356H
Submitting Materials for Advisory Comments

- **Cover letter**
  - state request for advisory comments, with contact information (name, title, address, phone, fax, and email)
  - "Request for Advisory Comments" in subject line
  - List each promotional material individually
  - Include material type (2253 code) for each piece

- **Draft promotional materials including annotations to references**

- **Annotated supporting references**

- **Annotated current Approved Package Insert/Medication Guide/Patient Package Insert**
Advice within FDA

Provide consultation on:

– Prescribing information
– Cartons and product labels
– Medication Guides
– Patient Package Inserts (PPIs)
– Dear Healthcare Provider letters
– Pharmacoeconomics, health-related patient-reported outcome protocols
Surveillance and Enforcement
Surveillance

• Review materials submitted to OPDP at time of initial dissemination
  – Sponsors must submit on Form FDA 2253
  – OPDP receives ~80,000 unique pieces each year

• Conferences

• Complaints
  • Healthcare professionals
  • Consumers
  • Competitors
Compliance with FFD&C Act

- Must be consistent with approved product labeling
- Must be supported by substantial evidence
- Must not be false or misleading
- Must have balance between efficacy and risk information
- Must reveal all material information
What is False or Misleading?

• Better or more effective than has been demonstrated by substantial evidence
• Safer (fewer side effects, lower severity) than has been demonstrated by substantial evidence
• Comparative claims (better or safer than other products) without substantial evidence
• Misleading presentation of data
Limitations to Surveillance

• Regular surveillance activities include:
  – Monitor promotional materials sent in via 2253s
  – Monitor Medical Convention Exhibit Halls
  – Review complaints

• Limited ability to monitor certain types of drug promotion: physician offices and industry-sponsored dinner/lunch programs
  – Home-made promotional materials not submitted to FDA
Bad Ad Program

- FDA-sponsored outreach program designed to educate HCPs about the role they can play in helping FDA ensure that prescription drug advertising and promotion is truthful and not misleading.

- When HCPs recognize misleading drug promotion, they can help put a stop to it by reporting it to FDA.

  - Call
    - 855-RX-BADAD
  - Email
    - BadAd@fda.gov
Report Misleading Rx Drug Promotion

The prescriber can play an important role in ensuring that prescription drug advertising and promotion is truthful by recognizing and reporting misleading drug advertising and promotion.

Prescription drug advertising must:
- Be accurate
- Balance the risk and benefit information
- Be consistent with the prescribing information (PI) approved by FDA
- Only include information that is supported by substantial evidence or substantial clinical experience

What types of prescription drug promotion does the Office of Prescription Drug Promotion (OPDP) monitor?
- All written or printed drug promotional materials
- TV and radio advertisements
- Sales representative or company-sponsored speaker presentations

OPDP does not regulate promotion of:
- Over-the-Counter Drugs
- Dietary Supplements
- Medical Devices

Common Issues:
- Omitting or downplaying of risk
- Overstating the effectiveness
- Promoting uses not addressed in FDA-approved PI
- Misleading drug comparisons

BadAd@fda.gov • 855-RX-BADAD
Enforcement

• Untitled Letters/Notices of Violation
• Warning Letters
• Injunction/Consent decree
• Seizures/Criminal action
• Civil and monetary penalties

Warning and Untitled Letters

• Mitosol® (mitomycin for solution) Untitled Letter

• Zovirax® (acyclovir) Cream 5% Untitled Letter

• EpiPen® (epinephrine injection) Warning Letter
Mitosol® (mitomycin for solution)

- **Indication**: adjunct to ab externo glaucoma surgery
- **Contraindications**: hypersensitivity and use in pregnancy
- **W&P**: cell death, post-operative hypotony, lenticular change and cataract formation in phakic patients
- **Common AEs**: hypotony, hypotony maculopathy, blebitis, endophthalmitis, vascular reactions, corneal reactions, and cataract
**Mitosol: Violative Material**

**NOW AVAILABLE!**

**Remove the Variables**

**Eliminate Your Concerns**

**Consistency**

**Potency**

**Shelf Life**

**Safety**

**Sterility**

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturing Controls</td>
<td>Yes</td>
</tr>
<tr>
<td>Directions for Use</td>
<td>Yes</td>
</tr>
<tr>
<td>Assured Potency</td>
<td>Yes</td>
</tr>
<tr>
<td>Assured Dosing</td>
<td>Yes</td>
</tr>
<tr>
<td>Shelf Life</td>
<td>24 months</td>
</tr>
<tr>
<td>No &quot;Black Box Warning&quot;</td>
<td>Yes</td>
</tr>
<tr>
<td>Room Temp Storage</td>
<td>Yes</td>
</tr>
<tr>
<td>Closed Transfer</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Mitosol®**

*(mitomycin for solution)*

0.2 mg/vial

**Kit for Ophthalmic Use**

Mitosol® is the only FDA approved ophthalmic formulation of mitomycin. The Mitosol® Kit provides room temperature storage and an extended shelf life. Assured sterility, potency, and dosing along with closed transfer and qualified disposal ensures mitomycin for ophthalmology.

Visit us at [www.mobiustherapeutics.com](http://www.mobiustherapeutics.com)

1-877-EYE-MITO (1-877-393-6486)

Please see full prescribing information attached.

2012-001
Mitosol Untitled Letter: Violations Cited

- Omission and Minimization of Risk Information/Omission of Material Facts
  - Makes claims about safety, effectiveness, and use, but fails to disclose full approved indication or any risk information
  - Makes claims regarding dosing benefits, but fails to present dosing information material to safe use of drug
    - “Remove the Variables” in conjunction with the word “Dosing”
    - “Assured Dosing – Yes”
    - Mitosol requires reconstitution and reconstituted product is then fully saturated on sponges and applied and kept on treatment area for 2 minutes. Also must be used within one hour of reconstitution
Zovirax® (acyclovir) Cream 5%

- **Indication**: Treatment of recurrent herpes labialis (cold sores) in adults and adolescents (> 12 years old)
- **Contraindications**: Hypersensitivity
- **Precautions**: cutaneous use only (not in eye or inside the mouth or nose); potential for irritation and contact sensitization; effect not established in immunocompromised patients.
- **Common AEs**: dry lips, desquamation, dryness of skin, cracked lips, burning skin, pruritus, flakiness of skin, and stinging on skin
ZOVIRAX® Cream

ZOVIRAX® Cream (acyclovir) 5% is indicated for the treatment of recurrent herpes labialis (cold sore) in adults and adolescents (12 years of age and older).

ZOVIRAX® Cream should be applied 5 times per day for 5 days. Therapy should be initiated as early as possible following onset of signs and symptoms (i.e., during the prodrome or when lesions appear). For adolescents 12 years of age and older, the dosage is the same as in adults.

Important Safety Information
ZOVIRAX® Cream is intended for external use only and should not be used in the eye or inside the mouth or nose. ZOVIRAX® Cream has a potential for sensitization and contact sensitization. In clinical trials, the most common adverse reactions at the site of topical application occurred in less than 1% of patients and included dryness, desquamation, erythema, skin rash, itching, redness of skin, irritation, burning, stinging, or pruritus. Decrease in size and disappearance of lesions may be observed within 48-72 hours. ZOVIRAX® Cream has not been studied for any systemic adverse reactions.

The patient should be instructed to avoid exposure to sunlight and to use a sunblock or protective clothing when exposed to sunlight.

This site is intended for healthcare professionals within the United States only.

Important Safety Information

Please click here for full Prescribing Information.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.
Zovirax Untitled Letter: Violations Cited

• Overstatement of Efficacy
  – “PROVEN EFFECTIVE AT ANY STAGE, Even When Therapy Is Initiated Late”
  – Suggests Zovirax proven effective during stages 4 through 6 (ulcer or weeping, crust or scabbing, or healing stages)
  – According to the PI:
    • “Therapy should be initiated as early as possible following onset of signs and symptoms (i.e., during the prodrome or when lesions appear)”
    • 2 pivotal clinical trials: patients instructed to initiate treatment within 1 hour of signs or symptoms of lesion
Zovirax Untitled Letter: Violations Cited

• Unsubstantiated Superiority
  – Zovirax vs. Valtrex
    • Presentations suggest Zovirax clinically superior to Valtrex due to extended timeframe of treatment initiation
EpiPen (epinephrine)

• **Indication**
  – Emergency treatment of Type 1 allergic reactions including anaphylaxis to stinging insects, biting insects, foods, drugs ….
  – Intended for immediate administration in patients, who are determined to be at increased risk for anaphylaxis….
  – Intended for immediate self-administration as emergency supportive therapy only and are not a substitute for immediate medical care

• **Risk information - Patient Labeling**
  – When you have an allergic reaction (anaphylaxis) use the EpiPen … right away and immediately go to your doctor or emergency room for more medical treatment
CLIENT: MYLAN SPECIALTY L.P.
PRODUCT: EpiPen BRANDED
AGENCY: GSW NEW YORK
SPOT TITLE: "MAX/BRENDED/PEOPLE"
ISCI CODE: DYEP0011000
DURATION: 60 SEC
DATE: 04.03.2012
© 2012 MYLAN SPECIALTY L.P.
EpiPen Warning Letter: Violations Cited

• Overstatement of Efficacy
  • Suggests that EpiPen *alone* can provide assurance that a child who has a history of life-threatening allergic reactions does not need to worry or take precautionary measures to avoid exposure to allergens.

  • Suggests that a child who has a peanut allergy can take a chance eating a piece of birthday cake with unknown ingredients and feel completely free from worry about any potential risk of anaphylaxis if prepared with EpiPen.
DATE: 11.27.12

AGENCY: GSW Worldwide

CLIENT: MYLAN SPECIALTY L.P.

TITLE: EpiPen Corrective

ISCI: DYEP002000H

DURATION: :75

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Contact Us

- Phone: 301-796-1200
- Fax: 301-847-8444 or 8445

- http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm090142.htm
Where to Submit Materials

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