



# HORIZONS

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## Monitoring the Practice of Medicine and Off-Label Uses

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## Off-Label Usage

- Off-label use – the use of a drug or device for an indication not approved by the FDA
  - Specifically not in the approved labeling and indications for use
- Must strike a balance
  - Ensuring patient safety and effective treatment
  - vs.
  - Educating physicians and promoting innovation to improve the quality of care



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## Physician Practice of Medicine

- Prescribing off-label falls within “practice of medicine” and is not illegal for clinicians
  - Considered to be the standard of care in some medical fields
- The submission of an IDE or IND, or review by and IRB is not required if off-label use is based on physician decision, *unless*;
  - There is additional data collection, testing, etc.
  - Company sponsorship, even of single patient or “case-series”

## Regulation of Off-label Use: Federal Food, Drug, and Cosmetic Act

- A drug or device may not be sold without first obtaining premarket approval or clearance
- Manufacturer of “new drugs” must demonstrate to FDA that they are safe and effective for each intended use (21 U.S.C. 331 (d))
- FDCA prohibits distribution of misbranded drugs and devices (21 U.S.C. §331(b))
- “Misbranding” includes a label with information on uses that have not been approved as safe and effective or cleared
- Violations could result in warning letters, product seizure, recalls, civil penalties, criminal penalties

## Regulation of Off-Label Use: When Does a Violation of the FDCA Turn into a Violation of the False Claims Act?

- A company commits fraud against the government if its improper off-label promotion leads a physician to prescribe a product for off-label use and the government pays for the use
  - Liability is not limited to the person submitting the claim. Thus, the company and sales reps involved may also be liable.
  - Actual knowledge or “Reckless Disregard”
  - Penalty: Fine of \$5,000 to \$11,000 + Treble damages
  - All States required to have their own versions
- Anti Kickback Statutes (“Fraud & Abuse”) may also be implicated
  - Induce business payable by a federal health care program (i.e. Medicare, VA system, military hospitals)

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## Regulation of Off-Label Use: FDA’s Prior Regulation of Off-Label Use

- Section 401 of FDA Modernization Act (FDAMA, 1998) expired in September 2006:
  - Had created a “safe harbor” for manufacturers to disseminate article reprints if several conditions were met:
    - Must be seeking, or intend to seek, approval for the off-label uses discussed in the article (**and have completed studies required**)
    - Must submit to FDA a reprint for pre-dissemination review
    - Provide reports to FDA every 6 months
- FDAMA safe harbor rarely invoked by industry

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## Regulation of Off-Label Use: FDA's Draft Guidance on Off-Label Use ("FDA's Good Reprint Practices")

- February 15, 2008:
  - *Draft Guidance for Industry: Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices*
- "Articles that discuss unapproved uses of FDA-approved drugs and devices can contribute to the practice of medicine and may even constitute a medically recognized standard of care. This guidance also safeguards against off-label promotion."
  - Randall Lutter, FDA deputy commissioner for policy.
- Also includes a **safe harbor** if a company distributes reprints in accordance with the guidelines, FDA will not use the dissemination as evidence of the manufacturer's intent to promote an off-label use

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## FDA's Draft "Good Reprint Practices"

- Draft Guidance has significant changes from FDAMA Sec. 401
  - Provides greater latitude for disseminating articles on unapproved uses
  - Eliminates the requirement that companies must agree to seek FDA approval for the discussed use
  - **Guidelines do NOT apply to scientific or medical information disseminated in response to UNSolicited requests for information from healthcare professionals**

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## Regulation of Off-Label Use: FDA's Draft "Good Reprint Practices"

- To fall within the safe harbor, manufacturer may only disseminate either
  - Articles that are peer-reviewed and published by a journal using an editorial board and independent experts that review manuscripts or
  - Scientific or medical reference publications
- Reprints should not be part of a special publication funded in any part by a manufacturer of a product discussed in the article
- Scientific or medical reference publications should not be written, edited, excerpted, or published specifically for, or at the request of, a drug or device manufacturer

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## FDA's Draft "Good Reprint Practices": Reprint or Text That Can be Disseminated

- Information should be derived generally from adequate and well-controlled clinical trials that are considered scientifically sound, not false or misleading, and do not "pose a significant risk to the public health"
- The distribution of the following would NOT fall within the Good Reprint Practices:
  - Letters to the editor
  - Publication abstracts
  - Reports of Phase 1 trials in healthy subjects (Pilot Device Studies?)
  - Reference publications that contain little or no substantive discussion of the relevant investigation or data

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## FDA's Draft "Good Reprint Practices": Methods of Dissemination

- Reprint or text must be complete and not altered by the company distributing it
- Must have a permanent and prominent label disclosing:
  - Uses have not been FDA-approved or cleared;
  - Manufacturer's interest in the drug or medical device;
  - Any author known to have financial interest in the product/manufacturer or receiving compensation from the manufacturer;
  - Any person known to the manufacturer who has provided funding for the study
  - Any significant risks or safety concerns known to the manufacturer concerning the unapproved use that are not discussed in the article or text.
- Reprint or text should be accompanied by the product's approved labeling and comprehensive bibliography

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## FDA's Draft "Good Reprint Practices": Methods of Dissemination

- When the conclusions of the article called into question by another article, the reprint should be disseminated with the contrary article
- Reprints (or texts) must be distributed separately from promotional information
  - Sales reps should not attach any reprints or texts to promotional materials
  - Reprints should not be the subject of discussion between sales rep and physician during sales visit
  - If sales rep receives questions from the recipient about these materials, s/he should refer the questions to the medical/scientific officer or department
- Dissemination discussing off-label uses at medical or scientific conferences must be done away from promotional exhibit halls and should not be distributed during promotional speakers' programs

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## OIG and the Draft Guidance

- How much protection from OIG will the guidance offer if it is ever finalized?
  - As the Guidance is still in draft form, OIG does not need to apply it to their enforcement activities
- If the FDA proposal becomes final, then with respect to *current* marketing activities, the OIG would be bound to apply the new regulatory standards
- But many of the off-label investigations are historical.
  - Companies' actions are going to be measured against the laws and standards at the time when claims were submitted [to Medicare].

## Corporate Strategies for Monitoring the Practice of Medicine and Off-Label Uses:

**Rethink Corporate Structure**

## Initial Considerations

- How are company departments organized?
  - Sales should not be associated with R&D Programs and funding, physician educational programs/conferences
- Who is in charge of product promotion/information?
  - Is an appropriate Marketing, Medical and Regulatory team drafting and approving marketing information, or (in worst case) is it left to each individual sales rep?
- Is there a Medical Affairs department separate from Sales & Marketing?
- Do you have an appropriate Compliance department/program in place?

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## Create a Compliance Department

- Required by California law
- Headed by a Compliance Officer who has direct access to the president or CEO and legal counsel, and is separate from sales & marketing
- **Essential Functions:**
  - Develop a written company code of conduct
  - Make periodic reports to the board and CEO on compliance matters
  - Develop and participate in company training and educational programs
  - Hire third party for independent auditing
  - Participate with company counsel in making reports to federal agencies regarding any violations
  - Establish and provide approved scripts for sales reps

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## Establish a Method for Employees to Raise Potential Compliance Issues

- Toll-free anonymous compliance telephone line
  - Also consider exit interviews and periodic surveys with sales reps to learn about the marketing environment in general
- Notify employees of this program through periodic emails, prominent postings in common areas, etc.
- Incorporate procedures to protect anonymity of complainants and protect whistleblowers from retaliation
- Compliance Officer should gather information from disclosing individual and make a good faith inquiry into the allegations
  - Maintain a disclosure log and records internal inquiries and corrective actions

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## Corporate Strategies for Monitoring the Practice of Medicine and Off-Label Uses:

### Effectively Manage and Oversee Employees and Programs

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## Implement Appropriate and Continuous Training and Education Programs

- Must have sales training and education programs for all sales and marketing (including contractors interacting with physicians)
  - Must occur when hired and retrained periodically
- All new employees (and old employees for continuing training) must certify in writing that they received the required training
  - Compliance Officer should maintain copies of these certifications, as well as training program and materials distributed
- All training and education programs should be reviewed and updated annually by the Compliance Department

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## Educate on Indications for Use

- The current labeling requirements and indications for use should be well understood by sales and marketing staff
  - Training (testing) of new sales reps, periodic retraining
  - Role playing is an effective way to reinforce labeling
- Make sales reps aware of differences between FDA approved labeling and Local Medicare Policies
  - Local policies are generally more narrow than labeling, but occasionally there can be aspects that are broader

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## Establish Clear Guidelines for Sales Reps

- Evaluation and compensation should NOT be linked to **promotion** of off-label sales
- Prohibited activities:
  - Creating own marketing ads
  - Placing cold calls on off-label specialists
  - Sending unsolicited medical letters to physicians regarding off-label use
  - “Baiting” (Elicitation) to get questions about off-label use
  - Providing false or misleading responses regarding efficacy and whether the product has been approved by FDA for the off-label use
- Adopt, publish, and review with all employees disciplinary policy for compliance violations

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## Education and Training Programs

- Companies may not sponsor publications of off-label use
- Off-label use may not be discussed at company sponsored training and educational meetings
  - Difficult to monitor
  - Need close working relationship with Medical Marketing
  - Review agendas and presentations
  - Use accredited CME organizations
- Medical Affairs and MSLs may not discuss off-label uses, unless initiated by clinician
  - There is no safe harbor for MSLs to initiate discussions
  - Baiting/Elicitation techniques should not be employed

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## Promotional Materials

- Generally not acceptable to discuss or describe any off-label use in
  - Promotional materials (sales and marketing pieces)
  - Educational materials
  - Web site
  - Press releases
- Beware of custom pieces created by sales reps
- If an off-label use must be mentioned in a promotional material (e.g. a press release that lists clinical papers being presented) disclaimers must be used:
  - Use is for investigational purposes only
  - Has not been approved by FDA

## Corporate Strategies for Monitoring the Practice of Medicine and Off-Label Uses:

### Response to Inquiries Regarding Off-Label Use

## Develop Written Procedures for Responding to Physician Inquiries for Off-Label Use

- Designate a separate department for responding to physician off-label inquiries (e.g., Medical Affairs)
  - Require sales reps to immediately refer **all** off-label physician inquiries to this department
- Record all inquiries from physicians regarding off-label use
  - Identity of the physician and sales rep
  - Nature of the topic of the request (including exact language if made in writing)
  - Identification of any written materials provided to the physician

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## Corporate Strategies for Monitoring the Practice of Medicine and Off-Label Uses:

**Monitor Off-Label Use**

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## Tracking Sales, Adverse Events, and Off-Label Use

- Is the percentage of off-label prescriptions higher than the percentage of on-label prescriptions?
  - Track off-label prescriptions by
    - percentage
    - geographic region
    - sales rep
- Did physicians' prescriptions of off-label uses change after attending company conferences?
- Is the company receiving reports of new adverse events associated with different uses?
- Review significant trends with Compliance and Senior Management, take corrective action if appropriate

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## QUESTIONS?



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**Monitoring the Practice of Medicine and Off-Label Use: A Culture of Compliance**  
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## Monitoring the Practice of Medicine and Off-Label Use: A Culture of Compliance

- The Problem:
  - Enforcement of off-label promotion rules is increasing.
  - Promotion is a “field-based” activity.
  - Traditional R/A activities are “office based”.
  - An office based approach to monitoring off-label promotion will fail to find much of the real world of promotional activity.

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## Monitoring the Practice of Medicine and Off-Label Use: A Culture of Compliance

- The Solution: R/A professionals must adopt their styles to fit the *cultures* of:
  - Their employers or clients, and
  - The real world of field sales and marketing to develop a *Culture of Compliance*.

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## Monitoring the Practice of Medicine and Off-Label Use: A Culture of Compliance

- Employer/ Client culture depends on:
  - Degree of risk taking/aversion
  - Robustness of current company procedures, training and resources
  - Regulatory scrutiny of that company's promotional practices and addition or modification where necessary

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## Monitoring the Practice of Medicine and Off-Label Use: A Culture of Compliance

- The culture of a field sales force depends on:
  - The individual salesperson's professional experiences, including with other companies
  - The degree of pressure to make quota
  - The personal relationships among related groups of salespersons (regions, etc.)
  - The extent of management's control of promotion practices.

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## Monitoring the Practice of Medicine and Off-Label Use: A Culture of Compliance

- The responsibility of R/A professionals to assure proper promotional compliance thus requires:
  - Understanding the laws and regulations
  - Understanding the company's culture and resources
  - Access to salespeople
  - Constant training and reinforcement
  - Knowing when, and how, to say "No".

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## Monitoring the Practice of Medicine and Off-Label Use: A Culture of Compliance

- How does an R/A professional encourage a culture of compliance?
  - Assure senior management support, especially senior sales management
  - Adopt *realistic* procedures
    - Regulatory overkill simply leads to noncompliance and invites governmental scrutiny
  - Train, and train the trainers
  - Insist on a level playing field by competitors

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## Monitoring the Practice of Medicine and Off-Label Use: A Culture of Compliance

- How does an R/A professional encourage compliance (cont.)?
  - *Partner* with sales people
  - “Windshield time”
  - Encourage field requests for advice
  - Attend sales meetings
  - Role play
  - Explain and use Safe Harbor rules

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## Monitoring the Practice of Medicine and Off-Label Use: A Culture of Compliance

- All of this takes time, patience and focus
  - Bona-fide implementation goes a long way to avoid IG oversight, even where there are occasional mistakes.
  - Success enhances the reputation and effectiveness of R/A in all of its responsibilities.

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## Monitoring the Practice of Medicine and Off-Label Use: A Culture of Compliance

- Questions?

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