
Off-Label Use of Drugs and Devices – Investigative Issues

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Outline of Presentation

- I. What Does Off-Label Mean?
- II. Review Recent Settlements and Court Decision.
- III. Overview of Off-label Issues Facing Research Institutions.

I. What Does Off-Label Mean?

What is Labeling?

- Manufacturer of drug/device must show FDA that product is safe and effective for intended use.
- FDA approves drugs and devices for specific uses. The package insert or “labeling” describes the approved uses. FDA regulates what written materials a manufacturer can use to describe product’s uses.

How is Labeling Defined?

- “...All labels and other written printed or graphic matter (1) upon any article or any of its containers or wrappers (2) or accompanying such article.” Federal Food and Drug Cosmetic Act (“FFDCA”) § 201
- FDA defines “labeling” on promotional materials to include any thing manufacturer distributes, even if it did not author it (i.e., articles from medical journals).

What is Off-Label?

- An “off-label” use is one the FDA has not expressly approved, i.e. change in dosing, patient population, purpose.
- Food Drug and Cosmetic Act (“FDCA”) prohibits manufacturer from marketing or promoting drug or device for off-label use.

21 U.S.C. § 331(a), (d)

FDA Modernization Act of 1997 ("FDAMA") § 401

- Allows dissemination of peer-reviewed journal articles or texts comprising clinical, quality of life or health economic information for off-label uses of drugs and medical devices
- Disclosure statement requirement
- 60-day waiting period
- Must be seeking approval for off-label use or obtain an exemption
- Must be truly off-label use

What Can Providers Do?

- Off-label restrictions do not apply to physicians and other providers. They can exercise their independent medical judgment to use product off-label, within the parameters of accepted medical practice and patient consent.
- “Allowing physicians to prescribe drugs for such ‘off-label’ usage ‘is an acceptable and necessary corollary of the FDA’s mission to regulate [pharmaceuticals] without directly interfering with the practice of medicine.’”

United States ex rel. Franklin v. Parke-Davis, 147 F. Supp. 2d 39, 44 (D. Mass. 2001) (quoting Buckman Co. v. Plaintiffs’ Legal Comm., 531 U.S. 341, 350 (2001))

Criminal and Civil Liability For Off-Label Promotion

- Individual

- Park doctrine allows prosecution of any person in responsible position, even if they lacked knowledge or intent to violate the law.
- Felony for company and/or individual employees if violation is committed with “intent to mislead”.

- Corporate

- Primary liability: FDA, product liability
- Secondary liability: consumers, competitors, employees, shareholders

False Claims Act Theories of Liability Involving Drugs and Devices

- A medical device or drug may not be marketed or promoted for “off-label” uses, i.e., uses that have not been approved by the FDA
- Government and whistleblowers allege that companies cause filing of false claims by “misbranding” products and promoting unapproved uses. For example, they may claim that the following cause false claims:
 - sponsorships of medical education programs, payments to attend advisory board meetings concerning off-label uses, off-label discussions with medical liaisons, and poorly drafted marketing materials

FCA Theories of Liability Involving Drugs and Devices (cont'd)

- Kickbacks disguised as consulting agreements, or legitimate educational grants, or research grants.
- Also, a payment to a customer can be characterized as a hidden discount in violation of the False Claims Act and Anti-Kickback Law. If offered as part of contract negotiations, the following may be characterized as improper discounts:
 - Consulting fees for undocumented services without a legitimate business purpose
 - Unrestricted educational grants
 - Purchases of unnecessary clinical research involving company's products
 - Purchases of sales data which is publicly available for lower costs

Conflicts of Interest?

Research institutions face a variety of issues that arise from a common concern about research into off-label uses: has a manufacturer biased their judgment so as to compromise their decisions, or to render them incomplete.

BASES FOR FRAUD ALLEGATIONS IN CLINICAL RESEARCH

- Failure to obtain IRB approval/misrepresentations to the IRB
- Incomplete or erroneous information in the informed consent process
- Failure to disclose and/or manage conflicts of interest
 - Individual
 - Financial/Associational
 - Institutional
 - Financial/Affiliated individual stands to gain personally
- Improper inducements by industry

EXAMPLE: INSTITUTIONAL OR INDIVIDUAL CONFLICTS

- Theory of liability: Defective product
 - Government paid for a research product (i.e., data)
 - The product lacks integrity because of a conflict of interest that undermines its reliability
 - Claim for payment for a defective product is a false claim

AAMC Principles for Protecting Integrity In the Conduct and Reporting of Clinical Trials

- Approved by Association of American Medical Colleges Executive Board on January 6, 2006
- Recommends full disclosure of participation in drafting and publication activity of employees of the clinical trial sponsor
 - “Authorship implies independent, substantial, and fully disclosed participation in the study and in the preparation of the manuscript.”
- “Investigators should fully disclose, and journals should publish, the existence of all relevant financial interests, including consultancies of any investigator, in all communications of trial results.”

Anti-Kickback Law

- Knowingly and willfully offering, paying, soliciting or receiving any remuneration (direct or indirect, in cash or in kind) in order to induce any person to purchase, order, or arrange for, or recommend the purchasing or ordering of products that may be paid for by Medicare, Medicaid or other Federal Health Care Programs
- Almost any payment or benefit given to a customer or potential customer could be viewed as payment for business if it is substantial enough to affect the recipient's judgment

When Does Remuneration Constitute Illegal Inducement?

- If even *one purpose* of a payment or other remuneration is to induce referrals for items or services reimbursed by federal programs, the remuneration violates the Anti-Kickback Law (U.S. v. Greber, 760 F.2d 68 (3d Cir. 1985), overruled on other grounds, U.S. v. Gaudin, 515 U.S. 506 (1995))
- Courts do not require proof of an explicit agreement to pay for business in order to find an improper inducement
- However, at least one appellate court has recognized that the mere hope for or expectation of referrals collateral to a legitimate motive for the financial arrangement does not rise to the level of improper inducement (U.S. v. McClatchey, 217 F.3d 823 (10th Cir.), cert. denied, 531 U.S. 1015 (2000))

AdvaMed Code of Ethics on Interactions with Health Care Professionals and Pharma Code

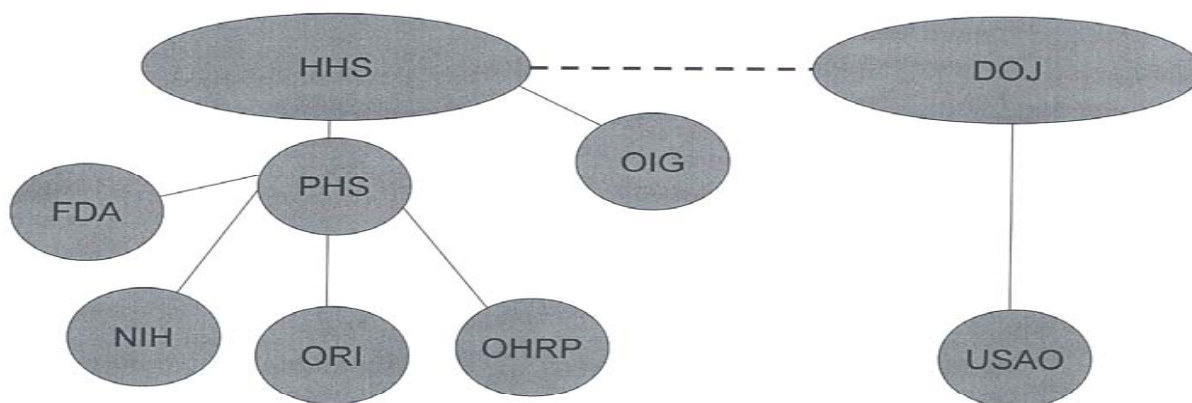
- The AdvaMed Code of Ethics on Interactions with Health Care Professionals was effective 1/1/04 for AdvaMed members
- “Health Care Professionals” include non-clinical people who make product-related decisions
- Pharma Code puts strict limits on gifts and benefits to physicians
- Both Codes provide some bright line standards that help guide Anti-Kickback Law compliance efforts
- Compliance with the Codes, along with an active compliance program, will be viewed favorably by the OIG and DOJ when evaluating arrangements outside the safe harbors

AdvaMed Code of Ethics

- Topics Covered:
 - Member-Sponsored Product Training and Education
 - Supporting Third Party Educational Conferences
 - Sales and Promotional Meetings
 - Arrangements with Consultants
 - Gifts
 - Reimbursement Support Programs
 - Grants and Other Charitable Donations

II. Recent Settlements and Court Decision

WHO'S WHO IN CLINICAL RESEARCH FRAUD



Recent Settlements

- Schering-Plough: \$435 million civil and criminal fine/penalty/refund for off-label promotion of Temodar and Intron-A and pricing of Claritan
 - Strong basis for medical benefits of off-label use
 - Civil settlement focuses on spending to generate “buzz” but not included as kickbacks in indictment
 - Extensive five year CIA to oversee sales/marketing and financial relationships with physicians

Recent Settlements

- Serono: In October 2005 Serono pled guilty and paid \$716 million civil and criminal fine/penalty/refund for off-label promotion of human growth hormone (Serostin).
 - Alleged Kickbacks to frequent prescribers – Cannes Trip
 - Alleged off-label use of BIA diagnostic equipment to calculate body mass and promote use of hormone for testing AIDs patients
 - Alleged Off-label marketing of hormone to HIV patients
 - Company signed 5-year CIA/subsidiary excluded for 5 years
 - Individuals criminally charged

U.S. ex rel Philip Hess v. Sanofi-Synthelabo Inc.,
2006 U.S. Dist. LEXIS 22449 (E.D. Mo. 2006)

- Qui tam action under FCA alleging fraudulent scheme to promote sale of drugs for “off-label” uses which caused submission of false claims for Medicaid reimbursement
- Federal court dismissed claims because of the absence of falsity in the presentation of data by the defendants and the lack of lies by the doctors who applied for Medicare reimbursement
 - “Innocent mistakes and negligence are not offenses under the Act . . . In short, the claim must be a lie.”
- Also found that plaintiffs did not meet the higher pleading standard as was the case in Parke-Davis

III. Overview of Off-Label Issues Facing Research Institutions

Issue 1

When Does Clinical Care Become Research?

- Doctor uses product off-label multiple times, gathers data and presents paper.
- Is this research without complying with standard protocols – IRB supervision, proper consent?
- How does one draw line between treating patient and cataloging knowledge?

Issue 2

Who Sponsors Research?

- Investigator sponsored research – Investigator is the sponsor and is responsible to FDA.
- Industry sponsored research – Company is the sponsor and hires investigator to carry out.

Issue 2 (cont'd)

What Happens When Company Makes Grant to Investigator to Support Study?

- Is Company circumventing FDA's supervision over Sponsor?
- Does Company intend grant to generate excitement and promote off-label uses?

21 CFR 312.7 Promotion for Investigational Drugs

- “A sponsor or investigator, or any person acting on behalf of a sponsor or investigator, shall not represent in a promotional context that an investigational new drug is safe or effective for the purposes for which it is under investigation or otherwise promote the drug.”

21 CFR 312.7 Promotion for Investigational Drugs (cont'd)

- “This provision is not intended to restrict the full exchange of scientific information concerning the drug, including dissemination of scientific findings in scientific or lay media. Rather, its intent is to restrict promotional claims of safety or effectiveness of the drug for a use for which it is under investigation to preclude commercialization of the drug before it is approved for commercial distribution.”

Safety and Efficacy Claims

- Standard for demonstrating safety and effectiveness is substantial evidence shown by “adequate and well-controlled investigations” (FFDCA § 505)
- Adequate and Well-Controlled Investigations: 21 CFR § 314.126
 - Clear statement of the objectives
 - Summary of proposed methods of analysis
 - Design permitting valid comparison with a control
 - Relevant population
 - Unbiased treatment group assignment
 - Well-defined study endpoints
 - Adequate disclosure of methods and results

Issue 3

Off-Label v. Unapproved Use

- Off-Label: device/drug approved for specific purpose, physician uses it same way for a different purpose or different population
 - Ex: Temoder approved for secondary treatment of specified brain tumors but effective for other brain tumors
- Unapproved: alter device/drug in a significant way, not just a tailor-made device
 - Ex: manipulate pacemaker to charge electrical current

Issue 3 (cont'd)

Provider Can Use Product Off-Label, But...

- FDA prohibits provider from using unapproved device

Issue 4

Who Pays?

(Government Revisiting This Rule)

- Medicare National Coverage Decision – encourage Medicare beneficiary to participate in clinical trials. Not reimburse for investigational device/drug, but pay for routine costs of qualifying clinical trials and reasonable and necessary services to diagnose and treat complications arising from participation in all clinical trials.
- www.cms.hhs.gov/coverage/8d2.asp

Coverage

- Medicaid pays for limited number of covered outpatient drugs.
- Will not pay for use that is not a medically accepted indication.
- Medically accepted indication = FDA approved use, or inclusion in drug compendia

MEDICAL DEVICE INDUSTRY ROLE IN CLINICAL RESEARCH FRAUD

Healthcare Purchasing News: Five hospitals settle cardiac device litigation - News Wire

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Five hospitals settle cardiac device litigation - News Wire

Five additional hospitals have settled allegations stemming from a nine-year-old whistleblower lawsuit on investigational cardiac devices. According to the settlement, Houston's Methodist Hospital receives \$2.75 million; Deaconess Medical Center, Spokane, WA, gets \$775,000; St. Luke's Episcopal Hospital in Houston receives \$575,000; Legacy Good Samaritan Hospital and Medical Center, Portland, OR, \$410,000; and Orlando (FL) Regional Medical Center, \$390,000. The settlements raise to more than \$45 million the total collected in the justice Department's ongoing investigation into the matter. The whistleblower lawsuit, filed by a former medical equipment sales rep, alleged that more than 100 hospitals had billed Medicare for procedures involving investigational cardiac devices, a practice that was illegal under Medicare's rules at the time. Twenty-nine other hospitals have settled similar allegations and 40 cases are outstanding.

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Issue 5

Is Off-Label Study a Disguised Kickback?

- Is Grant FMV Payment for Study?
- Could a Government Audit Challenge Budget Allocations or Actual Expenditures?

Draw Bright Lines

- Clearly define purpose of grant and research at beginning (valid study, generates valuable data)
- Make sure you follow the plan (publish data)
- Do not spoil legitimate grant with improper behavior

Issue 6

Pharma Sponsored CME?

- How much influence does Company have?
- Is it vehicle to generate buzz for off-label use?
- Need to have free market of ideas