



“Off-Label” Use Versus Clinical Trial Use of Devices: FDA Regulatory Issues

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“Off-Label Use”

- **Uses that do not appear in a device’s FDA-approved or cleared labeling.**
- **Uses that have not been approved or cleared by the agency.**
- **Presupposes that the device in question is approved or cleared for some use by FDA.**



“Off-Label Use”

- **Congress and FDA must balance:**
 - The need to regulate manufacturer promotion of “off-label” use of devices; and
 - The need for and availability of reliable scientific data and information regarding “off-label” use of an approved or cleared device.

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“Off-Label Use”

- Congress did not intend for FDA to interfere with the practice of medicine.
- FDA does not generally regulate how, and for what uses, physicians prescribe a cleared or approved device i.e., the practice of medicine.
- FDA recognizes that, in certain circumstances, “off label” use is appropriate, makes sense and is accepted as recognized medical practice.

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“Off-Label Use”

- The FDA Modernization Act of 1997 (FDAMA) recognizes appropriate device “off-label” use by statute in its codification of the historical “practice of medicine” policy.

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“Off-Label Use”

- FDA sees risks for the practitioner and patient:
 - Lack of labeling information, e.g., instructions for use, warnings and contraindications;
 - Lack of training;
 - Lack of balanced information;
 - Lack of follow-up care criteria or metrics; and
 - Sufficiency of the patient’s informed consent.

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Marketing and Promotion of “Off-Label” Uses

- FDA believes that allowing manufacturer promotion of “off-label” uses can have negative public health consequences.
- Discourages firms from submitting marketing applications for new product uses.
- No incentive to conduct clinical trials to support the safety and efficacy of “off-label” uses.

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Marketing and Promotion of “Off-Label” Uses

- Not all “off-label” uses may be safe and effective.
- Permitting manufacturer promotion of “off-label” use, based on studies reported in journal articles or other text, is not acceptable where the studies may be an inadequate basis for approval or clearance by FDA.
- May have disastrous consequences.

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Marketing and Promotion of “Off-Label Uses”

- Physicians may not receive a balanced view of the available information.
- Publication bias
 - Favorable results have a greater likelihood of being published.
 - Firms have no incentive to disseminate information recommending against a particular use.

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Regulatory and Civil Liability

- Untitled and Warning Letters
 - FDA seeking voluntary compliance
- Monetary penalties
- Criminal prosecution

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Exceptions

- **Modified medical devices that are the subject of a pending 510(k) submission for a new use.**
- **Unsolicited requests for information regarding off-label uses**
 - **Response must present both risks and benefits;**
 - **Response must be non-promotional in nature; and**
 - **Request must originate with the physician and not be “encouraged” by the manufacturer.**

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Scientific and Medical Journals

- **“Good Reprint Practices”**
 - **FDA has published a guidance document with regards to the distribution of medical journal articles and scientific or medical reference publications that discuss unapproved uses for approved or cleared medical devices**
 - **“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” (January 2009)**

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Industry-Supported Scientific and Educational Activities

- **FDA Guidance**
 - **"Guidance for Industry, Industry-Supported Scientific and Educational Activities"**
(November 1997)
 - **Considerations that the agency uses to decide whether an activity is independent of the influence and bias of the manufacturer or marketer or is promotional in nature.**

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Industry-Supported Scientific and Educational Activities

- **FDA will consider:**
 - **Who has control over the planning and content;**
 - **Who has control over the selection of speakers;**
 - **Appropriate control of relationships;**
 - **Overall intent to produce an independent and non-promotional educational activity;**

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Industry-Supported Scientific and Educational Activities

- **FDA will consider:**
 - **Whether employees of the activity provider have any connection to the manufacturer;**
 - **Provider's prior history;**
 - **Multiple presentations;**
 - **Who generates the mailing list;**
 - **Opportunity for meaningful discussion or questioning; and**
 - **Information disseminated during or after the meeting.**

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Promotion by Physicians

- **A physician may present educational information about an approved or cleared use of a medical device on a manufacturer's behalf.**
- **A physician may speak about off-label uses during activities which FDA considers non-promotional and educational.**

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Promotion by Physicians

- Physicians may cross the line if the activities give FDA the impression that the physician is promoting off-label uses on behalf of the manufacturer or marketer.

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Promotion by Physicians

- Physicians may be at risk of sanction for violation of the FDCA.
- “Off-label” promotion of a device may cause the product’s adulteration or misbranding and in turn a prohibited act.
 - 21 U.S.C. § 331(a)
 - 21 U.S.C. § 331(b)
 - 21 U.S.C. § 331(k)

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Promotion by Physicians

- **Devices may become adulterated or misbranded if:**
 - **Statements cause the labeling to become false or misleading;**
 - **Statements cause the device not to bear adequate directions for use or warnings; or**
 - **Change or modification in intended use is made where additional marketing approval or clearance is required but not obtained.**

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Penalties for Prohibited Acts

- **Civil money penalties of up to \$15,000 per violation;**
- **Prosecution of misdemeanor or felony violations of the FDCA;**
- **Injunction;**
- **Disqualification from participating in medical device clinical trials; or**
- **Warning Letters.**

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Appropriate “Off-Label” Use

- Use must involve a device that is approved or cleared for some use.
- There has to be a legitimate healthcare practitioner-patient relationship.
 - Cannot sell devices for “off-label” use to persons who are not patients
 - Cannot promote “off-label” use to the public
 - Cannot actively recruit new patients through promotion of “off-label” uses

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Dissemination of Information

- FDA generally does not prohibit the dissemination of “off-label” information to healthcare professionals by independent parties other than device firms.
 - Compendia
 - Journal articles
 - Impartial continuing education programs
 - Professional conferences
 - Databases

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Investigational Devices

- The regulation of investigational device use is governed by 21 U.S.C. § 360(j)(g).
“It is the purpose of this subsection to encourage to the extent consistent with the protection of the public health and safety and with ethical standards, the discovering and development of useful devices intended for humans and to that end maintain optimum freedom for scientific investigations and their pursuit of that purpose.”

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Investigational Devices

- The implementing regulations are called the Investigational Device Exemptions (IDE) regulations and are found at 21 C.F.R. Part 812.
- An IDE:
 - Balances scientific exploration and innovations with safety considerations.
 - Encourages the discovery and development of medical devices.
 - Puts controls in place to assure the adequate safety and effectiveness of investigational devices and protection of human subjects.

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Investigational Devices

- An IDE allows a sponsor to ship devices for investigational use in clinical trials.
- The device is usually used in a well-controlled clinical study designed to support a premarket submission.
- Use of an investigational device is limited to the clinical investigators identified by the sponsor.
- IRB approval/informed consent.

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Other Regulations

- Other regulations apply to clinical trials involving investigational uses of devices:
 - 21 C.F.R. Part 50 Informed Consent
 - 21 C.F.R. Part 54 Financial Disclosure
 - 21 C.F.R. Part 56 Institutional Review Board

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Parties Involved in Clinical Research

- Sponsor
- Investigator
 - Principal investigator
 - Co-investigators
- Institutional Review Board (IRB)
- Study subject
- Study monitor

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Types of Investigational Device Use Studies

- Significant risk – any device which in some way presents a potential for serious risk to the health, safety or welfare of subjects.
- Non-significant risk – devices which do not meet the “significant risk” criteria.

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Sponsor's Responsibilities

- Significant risk studies
 - FDA approval of an IDE application
- Non-significant risk studies
 - Abbreviated IDE requirements as defined by 21 C.F.R. § 812.2(b)
 - Labeling per 21 C.F.R. § 812.5

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Sponsor's Responsibilities

- IRB approval
- Selection of investigators
- Selection of monitors
- Investigator agreements and compliance
- Device control
- Investigational plan

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Sponsor's Responsibilities

- Evaluation of unanticipated device events
- Records and reports
- Labeling
- Prohibition against promotion and commercialization

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Recruiting Study Subjects

- A sponsor may advertise for research subjects and investigators.
- FDA has issued guidance on how this is to be done.
 - “Information Sheet - Guidance for Institutional Review Boards and Clinical Investigators (Recruiting Study Subjects)” (May 2009)

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Responsibilities of Investigators

- Investigators must conduct the investigation in accordance with the:
 - Signed investigator agreement
 - Investigational plan
 - IDE regulations
 - Any conditions of approval imposed by the IRB or FDA

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Responsibilities of Investigators

- Primarily responsible for obtaining informed consent from each subject before beginning the study
- Can only permit use of the device with subjects under his/her direct supervision
- Must return any remaining supply of the device at the termination of the study
- Financial disclosure
- Records and reports

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Responsibilities of IRBs

- Approves, requires modifications for approval, or disapproves clinical investigations
- Assures that appropriate steps are taken to protect the rights, safety, and welfare of human subjects
 - Initial and periodic review
- Uses a group process to review

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Common Regulatory Problems

- Lack of IRB approval/periodic review;
- Failure of clinical investigators to submit periodic reports or study modifications to the IRB;
- Inadequate procedures to ensure conformance to informed consent requirements; and
- Use of the investigational device outside the FDA-approved clinical protocol.

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FDA Oversight

- Speed and transparency of FDA actions
- GAO report
- “The Strengthening of FDA Integrity Act of 2009”
- Bioresearch monitoring

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Sponsor Noncompliance Issues

- Failure to secure investigator compliance with the signed investigator agreement, the investigational plan, applicable FDA regulations and/or other IRB or FDA conditions of approval;
- Failure to ensure adequate monitoring of investigations and failure to have written procedures for monitoring;

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Sponsor Noncompliance Issues

- Failure to accurately document device shipment records;
- Failure to prepare and submit progress reports as required to FDA and the reviewing IRB; and
- Failure to obtain adequate signed investigator agreements for each investigator participating in a study.

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IRB Noncompliance Issues

- Failure to conduct initial and continuing review of research at least annually and failure to follow written procedures for the same;
- Failure to assure that the IRB reviews proposed research at convened meetings at which a majority of the members are present;
- Failure to prepare and maintain adequate documentation for IRB activities, including minutes of IRB meetings;

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IRB Noncompliance Issues

- **Failure to have adequate written procedures governing the functions and operations of the IRB;**
- **Failure to assure that information given to subjects as part of informed consent is compliant; and**
- **Failure to follow written procedures for ensuring prompt reporting to FDA of any unanticipated problems involving risk to human subjects or others.**

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Investigator Noncompliance Issues

- **Failure to adhere to informed consent requirements, including obtaining IRB approval prior to requesting informed consent of a subject;**
- **Failure to conduct an investigation according to the signed agreement, the investigational plan, and applicable FDA regulations;**

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Investigator Noncompliance Issues

- Failure to obtain approval prior to implementing a change to the investigational plan;
- Failure to maintain accurate, complete and current records related to participation in the investigation;
- Failure to ensure proper oversight of the investigation;

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Investigator Noncompliance Issues

- Failure to submit progress reports on the investigation to the sponsor, monitor, and reviewing IRB at regular intervals but at least yearly; and
- Failure to maintain accurate, complete and current records of receipt, use or disposition of a device that relate to the type and quantity of the device, the dates of receipt and the batch numbers.

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Disqualification of Investigators

- Imposed if FDA determines that a researcher has repeatedly or deliberately not followed the rules intended to protect study subjects and to ensure data integrity.
- FDA can also take this step if a clinical investigator has deliberately or repeatedly submitted false information to the agency or the sponsor in a required report.

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Disqualification of Investigators

- FDA bioresearch monitoring inspections
 - Form FDA-483 or Warning Letter
 - Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE) letter
- FDA keeps lists of clinical investigators who have been disqualified and/or who have had compliance issues.
 - Posted on FDA's website

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“Off-label” v. Investigational Use

- **Use of a marketed device for a use not in the approved or cleared labeling when the intent is the “practice of medicine” does not require the submission of an IDE application or other IDE compliance.**
- **When the principal intent of the investigational use of a device is to develop information about the product’s safety and efficacy, IDE compliance is required.**

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Avoiding Corporate or Personal Liability

- **Understand FDA requirements**
 - **FDA guidance documents**
- **If a physician, don’t rely on a device manufacturer or marketer to assess whether an activity is appropriate**
- **Understand what factors may increase the likelihood that FDA would take adverse action**

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Questions?

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