Clinical Trials of Off-label Drug Uses: A Regulatory Minefield

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What are "Off-label" Uses?

- Unapproved *use* of an FDA-approved drug
  - FDA has approved the drug for other uses

- Distinguish from unapproved *drugs*
  - FDA approves "new drugs" for specified uses based on safety and effectiveness data submitted in a New Drug Application (NDA)
  - Phase I, II and III clinical trials: studies of previously untested drugs. 21 CFR § 312.21.
  - Drug labeling may include only *approved* uses

What are "Off-label" Uses?

- Labeling = labels and written materials on or accompanying product
- Unapproved uses = "off-label" uses
- Claims of unapproved uses in labeling = "false or misleading."
- False or misleading labeling = "misbranded" drug
- Selling, receiving or manufacturing a misbranded drug = prohibited act.

Off-label Uses of Approved Prescription Drugs

- Physicians may *prescribe* an approved drug for off-label uses if medically reasonable and necessary
  - Common practice in oncology
  - FDA does not regulate the practice of medicine
- But FDA allows only limited *advertising* by manufacturers of off-label uses of approved drugs
  - General rule: Advertising for an approved prescription drug is limited to uses approved for product labeling. 21 CFR § 202.1(e)(4).
  - Very limited dissemination of information regarding off-label uses. FDCA § 551-2.

FDA Approval of New Uses of Approved Prescription Drugs

- FDA expects manufacturers to seek approval for new uses
- New use = "new drug"
- Manufacturers can submit a supplement to NDA for new uses
  - Have safety data from initial Phase I clinical trials
  - Need data to demonstrative effectiveness for new uses
  - Sources of data:
    - Record reviews by physicians who prescribe for off-label uses
    - New clinical trials

FDA Approval of New Uses of Approved Prescription Drugs

- "Phase IV" studies
  - Post-marketing studies of *approved* uses
    - Sometimes required by FDA as a condition of approving an NDA. (21 CFR § 312.85)
    - Obtain additional information about different
      - Doses
      - Routes of administration
      - Patient populations
      - Stages of disease
  - Clinical trials of *off-label* uses

Phase IV Studies of Off-label Drug Uses

- Phase IV studies of off-label uses pose many regulatory concerns
- Concerns are greatest for Phase IV studies of off-label uses in which sponsors do not intend to use the data to seek FDA approval for new use
  - Is this "research" or "promotion" of off-label uses?
  - Reimbursement issues
    - Will study drug be provided by sponsor free or at a discount?
    - Will Medicaid or Medicare be billed for study drugs?
      - Reimbursement of free/discounted drugs may = false claim
      - If intended to induce doctors to prescribe for off-label uses may = anti-kickback violation

Suspect Phase IV Clinical Trials

- Many research sites with relatively few subjects at each site
  - Phase III: 30 sites x 100 subjects/site =
    - 3000 subjects
    - 30 physician/investigators
  - Phase IV: 500 sites x 6 subjects/site =
    - 3000 subjects
    - 500 physician/investigators
- Compliance concerns
  - Administratively more costly to enroll 3000 subjects at 500 sites than 30 sites. Why choose this model?
  - Is study designed to influence prescription of study drug by physicians in many markets?

Suspect Phase IV Clinical Trials

- **The OIG* has identified Phase IV studies as problematic**
  - **"Post-marketing research activities should be especially scrutinized to ensure that they are legitimate and not simply a pretext to generate prescriptions of a drug."**
  - **"Indicia of questionable research include . . . Post-marketing research used as pretense to promote product.**

***OIG Compliance Guidance for Pharmaceutical Manufacturers, April 2003**

Suspect Phase IV Clinical Trials

- Phase IV clinical trials may be used as evidence of healthcare fraud
- *U.S. ex rel. Franklin v. Pfizer Inc. and Parke-Davis, Div. of Warner Lambert Company* (D. Mass., Civil Action No. 96-11651)
  - *Qui tam* (whistleblower) case
  - Alleged manufacturer financially induced physicians to prescribe Neurontin (anti-seizure drug) for off-label uses
    - Violations of the Federal False Claim Act and Federal Anti-kickback Statute
  - Phase IV ("STEPS") clinical trial of Neurontin (anti-seizure)
    - Higher doses than approved by FDA
    - 1200 sites; 2-3 subjects/site
    - "Although STEPS took the form of a research clinical trial, it was, in fact, a marketing ploy * * *." (First Amended Complaint, 2002)

Phase IV Studies of Off-label Drug Uses

- Compliance Issues
  - FDA (Federal Food, Drug & Cosmetic Act (FDCA))
  - Healthcare fraud and abuse
    - Federal Anti-kickback Statute
    - Federal False Claims Act
- Regulators
  - FDA
  - Office of Inspector General (OIG)/DHHS
  - U.S. Department of Justice (DOJ)
  - State Attorneys General
  - Private lawsuits (*qui tam*, torts)

Phase IV Studies of Off-label Drug Uses: Compliance Concerns

- Phase IV clinical trials of off-label prescription drug uses create compliance concerns for:
  - IRB (45 CFR 46, 21 CFR 50, 56)
  - Research sites
  - Investigators
  - IRBs
  - Industry sponsors
- The number of Phase IV studies is expected to increase
  - Relatively fewer new drugs in the R&D pipeline
  - Increased focus on marketing new uses of approved prescription drugs

Clinical Trials of Off-label Drug Uses: FDA Issues

Question: Is an investigational new drug application (IND) required?

- **General rule: An IND is required for all "clinical investigations." 21 CFR § 312.2(a).**
  - **Clinical investigation: any experiment in which a drug is administered or dispensed to, or used by, ≥ human subjects.**
  - **Under § 312.2, "an experiment is any use of a drug except the use of a marketed drug in the course of medical practice." § 312.3(b).**
- **Unless an exception applies. § 312.2(b).**

Clinical Trials of Off-label Drug Uses: FDA Issues

An IND is *not* required if all of the following apply:

1. There is no intent to submit the results to the FDA for approval of a new use or other significant change in labeling;
2. If the drug is an approved prescription drug, there is no intent to use the results to support a significant change in advertising;
3. The study does not involve a route of administration, dosage level, subject population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with use of the drug [common with cancer drugs];
4. The study is conducted in compliance with 21 CFR Parts 50 and 56 (human subject protections, IRB function); *and*
5. The study is conducted in compliance with FDA requirements concerning promotion and charging for investigational drugs (21 CFR § 312.7)

Clinical Trials of Off-label Drug Uses: FDA Issues

- **Large, randomized studies generally need an IND**

- **"FDA believes that most randomized studies of a size that *could* support a labeling supplement would fall in the [non-exempt] category. (Emphasis added.)***

***** **FDA Guidance, *IND Exemptions for Studies of Lawfully Marketed Drug or Biological Products for the Treatment of Cancer*, 9/03.**

Clinical Trials of Off-label Drug Uses: FDA Issues

- Scenario #1 – easy case:
  - The manufacturer/sponsor intends to use study results to get FDA approval to add new uses to the product labeling.
- Analysis
  - An IND is required (do not meet exception criteria #1 and #2)
  - Who obtains the IND?
    - Usually the responsibility of the sponsor. 21 CFR § 312.20.

Clinical Trials of Off-label Drug Uses: FDA Issues

- **Scenario #2 – hard case:**
  - **The manufacturer/sponsor does *not* intend to get FDA approval for new uses**
  - **Results will be used to prepare an article for publication**
  - **Sponsor will not get an IND, and either:**

    (a) IND is *not* required, or

    (b) Investigator must get the IND as a precondition for doing the study
  - **What are the options and regulatory concerns for the research site?**

Clinical Trials of Off-label Drug Uses: FDA Issues

- **Scenario 2(a): Sponsor represents that an IND is not required.**
  - **What is research site's responsibility?**
  - **Does research site have exposure to liability if it accepts sponsor's decision w/o independent analysis? YES!**

Clinical Trials of Off-label Drug Uses: FDA Issues

Scenario 2(a), cont'd:

- **Analysis (research site):**
  - **Meets criteria #1 and #2 (labeling and advertising)**
  - **Study must be approved by IRB (criterion #4)**
    - **IRB is responsible for ensuring risks to subjects are minimized and reasonable relative to benefits**
  - **Criterion #5 – No promotion of unapproved uses**
    - **Sponsor's responsibility**
  - **Criterion #3 – Risk assessment**

Clinical Trials of Off-label Drug Uses: FDA Issues

#3. The study does not involve a route of administration, dosage level, subject population *or other factor* that significantly increases the risks (or decreases the acceptability of the risks) associated with use of the drug.

- **Who is responsible for criterion #3 risk assessment?**
  - **The FDA holds the investigator (who is responsible for administering the drug) responsible for assessing risk (see FDA Guidance on IND Exemptions, *IND Exemptions for Studies of Lawfully Marketed Drug or Biological Products for the Treatment of Cancer*, 9/03).**
  - **Based on investigator's professional judgment and knowledge of relevant literature**

Clinical Trials of Off-label Drug Uses: FDA Issues

- If research site determines an IND is not required, site should:
  - Obtain written documentation from investigator (PI) of risk assessment
  - Obtain an independent, second opinion from qualified professional
    - Does PI have a conflict of interest?
  - Obtain written documentation from sponsor of rationale for their belief that an IND is not required
    - Address all 5 criteria

Clinical Trials of Off-label Drug Uses: FDA Issues

Scenario 2(b): Sponsor requires the investigator to obtain an IND

- An investigator may submit an application to the FDA for an IND ("Investigator INDs")
- Concerns for research site
  - Why isn't sponsor obtaining the IND?
  - Who will prepare the IND?
    - PI may not have the time or expertise
    - Research administration may not have the technical expertise
    - Administrative and cost burden for research site. In research budget?
- What is the benefit to research site?

Clinical Trials of Off-label Drug Uses: FDA Issues

Scenario 2(b), cont'd: Possible benefits to research site

- **Authorship on publication**
  - **Who will write the article? Ghost written?**
    - **Ghost written articles have been cited as evidence of off-label promotion in lawsuits (e.g., *Parke-Davis*)**
  - **Is distribution of reprints "promotion" of off-label uses in violation of criterion #5?**
    - **#5. The studies will not be used to promote unapproved indications, in compliance with 21 CFR § 312.7.**
    - **21 CFR § 312.7(a). A sponsor, investigator, or any person acting on behalf of either, may not promote an investigational drug.**

Advertising Off-label Uses of Approved Drugs

- Under FDCA § 551-552, FDA allows limited dissemination of information about off-label uses
- Manufacturer may :
  - Respond to unsolicited inquiries by medical professionals
  - Disseminate reprints
    - Peer-reviewed article
    - Published in bona fide scientific or medical journals
    - Not false or misleading
    - Submitted to FDA at least 60 days prior to dissemination
- If manufacturer:
  - Has or is planning to submit a supplemental application to FDA for approval, *or*
  - Has a good reason why it should be exempted from getting FDA approval of new uses

Clinical Trials of Off-label Drug Uses: FDA Issues

Scenario 2(b), cont'd: Possible benefits to research site

- **FDA's restriction of off-label advertising is highly controversial**
  - **May FDA prohibit dissemination of truthful information?**
  - **First Amendment protection (scientific or commercial speech?)**
- **Liability**
  - **Neither sponsor nor investigator may "promote" off-label uses**

Clinical Trials of Off-label Drug Uses: FDA Issues

Scenario 2(b), cont'd: Possible benefits to research site

- **Availability of study drugs to site's patients**
  - **Study drug is available as an *approved* drug**
  - **Physicians may prescribe approved drugs for off-label uses for *treatment***
- **"Cost savings" from discounted or free study drug**
  - **BEWARE – fraud and abuse flags!**

Clinical Trials of Off-label Drug Uses: Fraud & Abuse Issues

- If Medicaid or Medicare will be billed for study drug, need to scrutinize for health care fraud and abuse issues
  - More common in Phase IV studies
  - Sponsor may represent "cost savings" as a benefit (incentive?) to research site
- Compliance Issues
  - Study drug not eligible for reimbursement
    - Federal False Claims Act
  - A purpose of the clinical trial is to induce prescriptions for off-label uses
    - Federal Anti-kickback Statute

Clinical Trials of Off-label Drug Uses: Reimbursement Issues

- **FDA**
  - **May not charge for an investigational drug tested in a clinical trial *under an IND* without prior FDA approval. 21 CFR § 312.7(d).**
  - **No ban on seeking reimbursement if study qualifies for an IND exception**

Clinical Trials of Off-label Drug Uses: Reimbursement Issues

- **Medicaid**
  - State dependent
  - Reimbursement
    - Of "covered outpatient drugs"
    - For a "medically accepted indication," defined as:
      - Approved under FDCA, or
      - Included in specified drug compendia
  - Prescription for *off-label* uses in clinical trials
    - Reimbursable *only* if listed in drug compendia

Clinical Trials of Off-label Drug Uses: Reimbursement Issues

- Medicare
  - Part A (institutional health care)
    - Covers drugs provided to inpatients
  - Part B (outpatient)
    - Covers
      - Administered by physician (or under physician's supervision) in physician's office/facility
      - Reasonable and necessary
    - Does not cover self-administered drugs
      - Typical clinical trial

Clinical Trials of Off-label Drug Uses: Reimbursement Issues

- **Medicare, cont'd.**
  - **National Coverage Decision for Clinical Trials (September 2000)**
  - **Covers "routine costs" for qualifying clinical trials**
    - **Standard care**
    - **Items/services required solely for the provision of the investigational item**
    - **Items/services necessary to diagnose/treat study-related complications**

Clinical Trials of Off-label Drug Uses: Reimbursement Issues

- **Medicare: NCD for Clinical Trials**
  - **"Routine costs" do NOT include:**
    - **Cost of the investigational drug itself, or**
    - **Items/services provided free by study sponsor**

Clinical Trials of Off-label Drug Uses: Reimbursement Issues

Coverage of off-label uses of study drug in clinical trials:

- **With an IND**
  - **Not reimbursable (FDA law)**
- **Without an IND**
  - **Inpatient or administered**
    - **Medicare: Yes (if reasonable & necessary)**
    - **Medicaid: No, unless listed in drug compendia**
  - **Outpatient, self-administered**
    - **Medicare: No**
    - **Medicaid: No, unless listed in drug compendia**

Fraud and Abuse Issues: False Claims Act

- **Federal False Claims Act, 31 U.S.C. § 3729-33.**
  - **Submission of false claims for reimbursement of study drug that:**
    - **Is not eligible for reimbursement**
    - **Was provided by sponsor *free* or at a discount**

Fraud and Abuse Issues: False Claims Act

31 U.S.C. § 1329(a)(1) ─ false/fraudulent *claims*

- **Any person who knowingly**
  - **Actual knowledge, or**
  - **Reckless disregard or deliberate ignorance of the truth or falsity of claim)**
- ***Presents* or *causes* to be presented**
- **A false or fraudulent claim**
- **To the federal government (e.g., Medicare or Medicaid)**
- **For payment or approval**

Fraud and Abuse Issues: False Claims Act

- FCA Penalties
  - Civil penalty: $5,000 - $10,000/claim
  - Treble the damages sustained by the U.S. Government
  - Attorneys' fees
- Whistleblower (qui tam) suits
  - Brought by private citizen (relator)
    - Recent increase in research-related suits
    - Relators: former collaborators, grad students/post-docs, sales/marketing reps
  - US DOJ may choose to intervene
    - If so, government litigates the case
    - Relator gets 15 – 25 % of judgment or settlement

Clinical Trials of Off-label Drug Uses: False Claims Act

Possible FCA violations in Phase IV trials

- **Billing federal government for ineligible off-label uses**
  - **". . .an off label prescription submitted for reimbursement by Medicaid is a false claim within the meaning of the FCA." *Parke Davis* (147 F. Supp.2d 39 (D. Mass. 2001)**
  - **Who may be liable?**
    - **Investigator and site: for knowingly *presenting* a false claim**
    - **Manufacturer/sponsor: for knowingly *causing* a false claim to be presented (*Parke-Davis*)**

Clinical Trials of Off-label Drug Uses: False Claims Act

- *Parke Davis*
  - Liability under the FCA is not limited to the party that submitted the false claim
  - Liability under the FCA reaches "all fraudulent attempts to cause the Government to pay out sums of money." (*citing U.S. v. Neifert-White Co.*, 1968)
  - "Relator has adequately alleged that Parke-Davis knowingly caused the submission of these false claims through a fraudulent course of conduct in violation of [the FCA]."
  - "The fact that such prescriptions are for an *off-label* use is material because . . . the government would not have paid [them] if it had known the use for which they were being submitted." (Emphasis added.)

Clinical Trials of Off-label Drug Uses: False Claims Act

Possible FCA violations in Phase IV trials:

- **Billing Medicaid/Medicare for study drug that was provided *free* or *discounted* by sponsor**
- ***U.S. ex rel. Hamel v. Fresenius Medical Care*, Civil Action No. 99-12455-NG (D. Mass)**
  - **Sponsor (Amgen) provided Epogen (dialysis drug) free to Fresenius' dialysis center for clinical trial**
  - **Fresenius submitted claims to Medicare and Medicaid for reimbursement of Epogen with the "study" designation intentionally removed**
  - **Defendant = research site (not sponsor)**
  - ***Qui Tam* lawsuit; US DOJ/Boston intervened**
  - **Case settled for $1.6M+ in January 2000**

Fraud and Abuse Issues: Anti-kickback Violations

- Fraud & abuse issues arise even if claims are not false or fraudulent
- Anti-Kickback Statute, 42 U.S.C. § 1320a-7b
  - Prohibits knowingly and willfully (intent)
  - offering, paying, soliciting or accepting
  - any remuneration (payments, honoraria, gifts, anything of value etc.) that
  - directly or indirectly induces
  - purchase of, or referrals for, healthcare
  - paid in whole or in part by federal programs.

Fraud and Abuse Issues: Anti-kickback Statute

- **Penalties:**
  - **Criminal**
    - **≤ $25,000 per offense**
    - **≤ 5 years in prison**
  - **Civil monetary penalties**
    - **Treble damages**
    - **Fines**
    - **Attorneys fees**
  - **Exclusion from Medicare/Medicaid**

Clinical Trials of Off-label Drug Uses: Anti-kickback Issues

- Anti-kick back issues in clinical trials of off-label uses
  - Will sponsor provide study drug for free?
    - If yes, and federal government not billed, then no AKS violation
  - If no, will federal payers (Medicare, Medicaid) be billed for drug?
    - If yes, = referral of patients by investigator to sponsor's drug, for which federal government will pay
    - Remuneration? Yes, compensation to research site by industry sponsor for study = "remuneration"
  - Is there intent to induce referrals or payment for healthcare?

Clinical Trials of Off-label Drug Uses: Anti-kickback Issues

- **Is there any intent to induce referrals or payment for healthcare?**
  - **Only needs to be *one* intended purpose**
    - **"a person who offers or pays remuneration to another person violates the [anti-kickback statute] so long as *one purpose* of the offer or payment is to induce Medicare or Medicaid patient referrals." (emphasis added) *U.S. v. McClatchey* (121 S.Ct. 574 (2000).**
  - **Prescriptions for sponsor's drug = referral**
    - **"[i]f funding is based, in any way, expressly or implicitly, on the physician's referral of the manufacturer's product, . . . the funding plainly implicates the anti-kickback statute." OIG Compliance Guidance for Pharmaceutical Manufacturers, 4/03**

Phase IV Clinical Trials: Fraud & Abuse Issues

OIG Guidance (4/03): Questionable clinical trials

- Initiated and/or paid by sponsor's sales or marketing departments rather than research dept./budget
- Not needed by manufacturer for any purpose other than the generation of business
  - If data will not be submitted to FDA for approval of a new indication for use, why not?
- Studies of questionable scientific value that provide substantial benefits to physician-investigators.
- Ghost-written articles
  - Investigator paid to use name as author on article written by manufacturer or their agent
  - Not fair market value for service provided

Clinical Trials of Off-label Drug Uses: Anti-kickback Issues

- Potential evidence of intent to induce referrals in clinical trials of off-label uses (if Medicare/Medicaid are billed)
  - Large number of research sites; few subjects/site
    - *Parke-Davis* – 1200 sites in Phase IV study of Neurontin
  - Significant payments to investigators for *de minimis* tasks
  - Compensation based on volume of referrals
    - Research contracts should be structured to fit in personal services safe harbor
    - Costs per subject should be based on FMV for services rendered and the same for all subjects
    - No finders fees or bonuses for subject recruitment

Clinical Trials of Off-label Drug Uses: Anti-kickback Issues

- **Who is liable?**
  - **Investigator and research site**
    - **For *accepting* kickback**
  - **Sponsor/manufacturer**
    - **For *offering* or *paying* remuneration**
- **Anti-kickback violation can be basis for FCA liability**
  - **Financial arrangement violates anti-kickback statute, and**
  - **There was a false express or implied certification of compliance (with AKS) to participate in Medicare or Medicaid**

Clinical Trials of Off-label Drug Uses: IRB Issues

- IRB is responsible for ensuring risks to subjects are minimized and reasonable relative to benefits (21 CFR § 56.111; 45 CFR § 46.111)
- Issues
  - Phase IV clinical trials conducted without an IND
  - Placebo arms
    - Example: subjects randomly assigned to study drug A, comparator drug B, or placebo
    - Use of placebo needs to be carefully reviewed when there are standard treatments available
  - Washout period (subjects stop taking current drug)

Clinical Trials of Off-label Drug Uses: IRB Issues

- IRB and individual members have been named as defendants in private and qui tam lawsuits
- *Scheer v. Burke et al.* (Phila., July 2003)
  - Alleged negligence against IRB chair and members for
    - Approving protocol
    - Approving the informed consent form
    - Failure to adequately monitor the conduct of the study (continuing review)
  - Duty based on federal regulations and informed consent form (ICF = contract)
  - Duty to protect subjects from "unethical research practices"

Clinical Trials of Off-label Drug Uses: Summary

- Clinical trials of off-label uses are important and can provide useful scientific information
- Regulatory issues require careful design and review of:
  - Experimental design
  - Budgets
  - Payment for study drug
- Need knowledgeable and coordinated compliance oversight by research sites
  - IRBs
  - Office of grants/contracts
  - Billing

Clinical Trials of Off-label Drug Uses: A Regulatory Minefield

Questions?