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 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
  - *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?
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

  - 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

  - 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
  - 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?