Taking a Deeper Dive: Regulatory Issues You Should Really Understand – Federal Regulation of Biomedical Research

The Pharma, Biotech & Device Colloquium

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Taking a Deeper Dive: Regulatory Issues You Should Really Understand

- **Carol Pratt: – Federal Regulation of Biomedical Research**
- **Joan Macaulay: Exchange of Scientific Information and Off-label Promotion**
- **Joseph Metro: Reimbursement and Payment Update**

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

The Regulatory Problem

- **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 *promotion* 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.**

Phase IV Studies of Off-label Drug Uses

- The OIG* has identified Phase IV studies as a potential vehicle for impermissible off-label promotion of approved drugs
  - "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

Phase IV Studies of Off-label Drug Uses: Regulatory Issues

- Suspect Phase IV clinical trials
  - Sponsors do not intend to use the data to seek FDA approval for new use. Why not?
  - 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

Phase IV Clinical Trials of Off-label Drug Uses: Regulatory Issues

- Is this "research" or "promotion" of off-label uses?
  - 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?
- Limited FDA enforcement tools
- Reimbursement issues
  - If federal government (Medicaid or Medicare) is billed for study related costs (drug or health care)
  - Reimbursement violations may trigger liability under Federal fraud & abuse laws
    - False Claims Act
    - Anti-kickback Statute
  - Big enforcement punch!

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

- If Medicaid or Medicare will be billed for study drug, need to scrutinize clinical trial for health care fraud and abuse issues
  - More common in Phase IV studies (approved drugs)
- Federal False Claims Act
  - Potential "false claims"
    - Study drug not eligible for reimbursement
    - Reimbursement of free/discounted drugs
      - May be represented as a "cost savings" to research site
- Federal Anti-kickback Statute
  - If an intended purpose of the clinical trial is to induce prescriptions for off-label uses

Fraud and Abuse Issues: False Claims Act*

- 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
  - Seeking reimbursement for a claim one "knows" is not eligible for reimbursement = "false" claim
- To the federal government (e.g., Medicare or Medicaid)
- For payment or approval

* 31 U.S.C. § 1329-33

Fraud and Abuse Issues: False Claims Act

- **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)**
    - **Relators: former collaborators, grad students/post-docs, sales/marketing reps – the danger is from *within*!**
    - **Recent increase in research-related suits**
  - **US DOJ may choose to intervene**
    - **If so, government litigates the case**
    - **Relator gets 15 – 25 % of judgment or settlement**

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

- False Claim Act violations
  - Submitting claims to federal payer for study drug that is not eligible for reimbursement
- Coverage of investigational drugs
  - 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: Is an IND Required?

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: Reimbursement of Investigational Drugs

- Medicare
  - Part A (institutional health care)
    - Covers reasonable and necessary drugs provided to inpatients
  - Part B (outpatient)
    - Covers reasonable and necessary drugs administered by physician (or under physician's supervision) in physician's office/facility
    - 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**
  - **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

- **Medicaid**
  - **Coverage varies by state**
  - **General rule: covers 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

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

- **With an IND**
  - **Not reimbursable (FDA)**
- **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**

Clinical Trials of Off-Label Uses: False Claim Act Issues

- **Billing federal government for ineligible off-label uses in Phase IV clinical trial may be a false claim**
- ***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**
    - **Relator was an MD who was a "medical liaison" for Parke-Davis**
  - **US DOJ alleged that manufacturer (Parke-Davis) used Phase IV clinical trial to promote off-label uses of Neurontin (anti-seizure drug)**
  - **Defendants were the *manufacturers***
    - **Research site, which submitted claims to Medicaid for reimbursement of Neurontin, were *not* defendants**
  - **Case settled in May 2004 for ~ $427 Million**

Clinical Trials of Off-Label Uses: False Claim Act Issues

***Pfizer*, continued:**

- **Phase IV ("STEPS") clinical trial of Neurontin**
- **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, 2003)**
- **Study sites submitted claims to Medicaid for Neurontin**
  - **"*. . .an off label prescription submitted for reimbursement by Medicaid is a false claim within the meaning of the FCA.*" *Pfizer/Parke-Davis*, 147 F. Supp.2d 39 (D. Mass. 2001).**

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

- **Who may be liable?**
  - **Investigator and site: for knowingly *presenting* a false claim**
  - **Manufacturer/sponsor: for knowingly *causing* a false claim to be presented (*Pfizer/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."**
    - **"Relator has adequately alleged that [defendants] knowingly caused the submission of these false claims through a fraudulent course of conduct in violation of [the FCA].**

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

- **False Claim Act violations**
  - **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 Statute

- 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 the
  - 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

- **Will Medicare or Medicaid be billed for study drug,?**
- **Remuneration? Yes, payments to research site = *remuneration***
- **Referral? Yes, prescriptions for sponsor's drug = *referral* of patients by investigator/physician to sponsor's drug**
- **Intent to induce referrals or payment for healthcare? Fact-specific answer.**
  - **There 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).**
  - **Large number of research sites; few subjects/site**
    - ***Pfizer/Parke-Davis* ─ 1200 sites in Phase IV study of Neurontin**

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**
  - **Paying or accepting an inducement for referrals is a false express or implied certification of compliance to participate in Medicare or Medicaid programs**
  - **Reimbursement under a false certification = "false claim"**

Clinical Trials of Off-label Drug Uses: Summary

- Clinical trials of off-label uses are important and can provide useful scientific information
- Regulatory minefield
- Require careful design and review of:
  - Experimental design (# of site and subjects)
  - Budgets
  - Payment for study drug

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

Questions?