Compliance Issues in Research-Related Relationships with Health Care Professionals

Pharmaceutical Compliance Forum:
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Overview

- Compliance History
- Current Compliance Concerns
- Compliance Environment
- Compliance Actions

Compliance History

- Longstanding Government Concern with Relationships between Pharmaceutical Manufacturers and Health Care Professionals (HCPs)
  - Department of Health and Human Services Office of Inspector General (OIG) Special Fraud Alert: Prescription Drug Marketing Schemes (Issued August 1994)
  - OIG Compliance Program Guidance for Pharmaceutical Manufacturers (May 5, 2003)
- Concern Addressed Sham Research Relationships and Need for Separation in Research and Marketing Activities

Compliance History

- Special Fraud Alert: Prescription Drug Marketing Schemes (Issued August 1994)

How Does the Anti-Kickback Law Relate to Prescription Drug Marketing Schemes?

. . . .Physicians, suppliers and, increasingly, patients are being offered valuable, non-medical benefits in exchange for selecting specific prescription drug brands. . . . .Among the specific activities, which the OIG has identified, are the following actual cases:. . . .

- *A ``research grant'' program in which physicians were given substantial payments for de minimis recordkeeping tasks. The physician administered the drug manufacturer's product to the patient and made brief notes, sometimes a single word, about the treatment outcome. Upon completion of a limited number of such ``studies,'' the physician received payment from the manufacturer.*

. . . . If one purpose of any of these marketing schemes is to induce the provision of a prescription drug item reimbursable by Medicaid, then the criminal anti-kickback statute is implicated. . . .

OIG investigation may be warranted where one or more of the following features is present in prescription drug marketing activities:. . . .

- *Grants to physicians and clinicians for studies of prescription products when the studies are of questionable scientific value and require little or no actual scientific pursuit. The grants may nonetheless offer substantial benefits based on, or related to, use of the product.*

Compliance History

- OIG Compliance Program Guidance for Pharmaceutical Manufacturers (May 5, 2003)

- **Clinical Trial Sponsorship:** *Manufacturers often contract with purchasers of their products to conduct research activities on behalf of the manufacturer on a fee-for-service basis. These contracts should be structured to fit in the personal services safe harbor whenever possible.* ***Payments for research services should be fair market value for legitimate, reasonable, and necessary services.*** *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.* ***Prudent manufacturers will develop contracting procedures that clearly separate the awarding of research contracts from marketing.*** *Research contracts that originate through the sales or marketing functions--or that are offered to purchasers in connection with sales contacts--are particularly suspect.*
- **Research Grants for Investigator-Initiated Research:** *Pharmaceutical manufacturers sometimes provide funding to their purchasers for use in the purchasers' own research. In many cases, the research provides valuable scientific and clinical information, improves clinical care, leads to promising new treatments, promotes better delivery of health care, or otherwise benefits patients. However, as with educational grants, if linked directly or indirectly to the purchase of product, research grants can be misused to induce the purchase of business without triggering Medicaid Best Price obligations. To reduce risk,* ***manufacturers should insulate research grant making from sales and marketing influences****.*

Current Compliance Concerns

- Objectivity in Medical Decisions
  - No illegal remuneration to HCPs that can taint clinical decisions
- Integrity in Product Approval/Research Process
  - Public and government not misled into thinking product is safer than product is
- Accuracy of Product Claims
  - Consumers and health care professionals not rely on misinformation

Compliance Environment: Generally

- Recent Enforcement Actions Address Research-Related Activities
  - HCP research relationships subject to scrutiny/enforcement
  - Settlements include specific and rigorous commitments regarding HCP research relationships
- Other Government Initiatives Focus on Research-Related Activities
  - Identify need for increased oversight of product development and approval process (including clinical trials)
  - Provide clarification of obligations of research sponsor and investigator
  - Implement enhanced monitoring and enforcement

Compliance Environment: Recent Enforcement Actions

- Allergan (2010)
  - Investigation by DOJ, OIG and States
  - Allegations
    - Company used clinical trials to pay physicians to prescribe off-label
  - Settlement Agreement
    - Criminal fine and forfeiture of $375 million and a $225 million civil settlement with United States and States
    - Guilty plea to criminal misdemeanor for misbranding drug in violation of the Food, Drug and Cosmetic Act
    - Corporate Integrity Agreement (CIA) (5 years) with specific obligations addressing research-related activities

Compliance Environment: Recent Enforcement Actions

- Allergan Corporate Integrity Agreement
  - Scope
    - Covered Persons include company personnel involved in contracting with HCPs to conduct post-marketing clinical trials and other post-marketing studies of products reimbursed under federal healthcare programs (Product Related Functions)
  - Obligations
    - Company must maintain policies and procedures addressing conduct of Product Related Functions in accordance with FDA and federal healthcare program requirements
    - Company must maintain policies addressing post-marketing clinical trials and studies (such as investigator-initiated trials (ITTs)) including: (1) decision to provide support for study, (2) manner in which support is provided, (3) support for publication of information about studies, and (4) uses made of publications about studies

Compliance Environment: Recent Enforcement Actions

- Allergan CIA Obligations
  - Company training and education must address FDA and federal health care program requirements related to Product Related Functions
  - Company subject to Independent Review Organization review which includes Product Related Functions
  - Company must develop monitoring program for non-promotional activities including research-related activities (Phase IV post-marketing studies and IITs)
    - Written agreements describing work, fees, compliance obligations
    - Payment in accordance with fair market value analysis
    - Annual budget plan reviewed by compliance for research-related activities
    - Needs assessment for each researcher engaged
    - Monitoring to ensure research work performed
    - Risk-based audits of research arrangements performed by compliance

Compliance Environment: Recent Enforcement Actions

- Allergan CIA Obligations
  - Public disclosure on website of HCP payments
    - Payments to be disclosed consistent with payments under Section 6002 of Patent Protection and Affordable Care Act
  - Registration of clinical studies on NIH website and posting of results on NIH website
  - Posting of post marketing commitments on company website

Compliance Environment: Recent Enforcement Actions

- Forest Laboratories (2010)
  - Investigation by DOJ, OIG, FDA and States
  - Allegations
    - Company distributed one drug without obtaining FDA approval (drug on market was subsequently determined to be “new drug” and was distributed contrary to FDA conditions for distribution of unapproved drug pending approval)
    - Company promoted two drugs for unapproved uses (pediatric use when drugs only approved for adult use)
      - Promotion of one drug included dissemination of positive results of one study on use of drug in adolescents while not discussing negative results of another study
      - Company implemented “seeding study” intending to induce participating physician investigators to prescribe the study drug

Compliance Environment: Recent Enforcement Actions

- Forest Settlement
  - Payment of $313 million in criminal fines, civil penalties and asset restitution to United States and States
  - Guilty plea by subsidiary to felony count obstructing justice, misdemeanor count of distributing unapproved drug in interstate commerce and misdemeanor count of distributing misbranded drug
  - CIA (5 years) with specific provisions addressing research-related activities

Compliance Environment: Recent Enforcement Actions

- Forest Corporate Integrity Agreement
  - Scope
    - Covered Persons includes company personnel involved in contracting with HCPs to conduct post-marketing and other clinical studies of products reimbursed under federal healthcare programs (Promotional and Product Related Functions)
  - Obligations
    - Company must maintain policies and procedures addressing conduct of Promotional and Product Related Functions in accordance with FDA and federal healthcare program requirements
    - Company must maintain policies and procedures addressing sponsorship of post-marketing studies such as ITTs including: (1) decision to provide support for IIT, (2) manner in which support is provided, (3) support for publication of information about IIT, and (4) uses made of publications relating to IITs

Compliance Environment: Recent Enforcement Actions

- Forest CIA Obligations
  - Company training and education must address FDA and federal health care program requirements related to Promotional and Product Related Functions
  - Company subject to Independent Review Organization Review which includes Promotional and Product Related Functions
  - Company must develop monitoring program for non-promotional activities including research-related activities (Phase IV post-marketing clinical studies including IITs)
    - Written agreements describing work, fees, compliance obligations
    - Payment in accordance with fair market value analysis
    - Annual budget plan reviewed by compliance for research-related activities
    - Needs assessment for each researcher engaged
    - Monitoring to ensure research work performed
    - Risk-based audits of research arrangements reported to compliance

Compliance Environment: Recent Enforcement Actions

- Forest CIA Obligations
  - Public disclosure on website of HCP payments
    - Payments to be disclosed consistent with payments under Section 6002 of Patent Protection and Affordable Care Act
  - Registration of clinical studies on NIH website and posting of results on NIH website
  - Posting of postmarketing commitments on company website

Compliance Environment: Recent Enforcement Actions

- AstraZeneca (2010)
  - Investigation by DOJ, OIG, FDA and States
  - Allegations
    - Company promoted psychiatric drug for unapproved uses by recruiting HCPs to serve as authors of articles largely prepared by medical literature companies about studies HCPs did not conduct
    - Company paid illegal remuneration to HCPs recruited to conduct studies for unapproved uses
  - Settlement Agreement
    - Payment of $520 million to United States and States
    - CIA (5 years) with specific obligations addressing research-related activities

Compliance Environment: Recent Enforcement Actions

- AstraZeneca Corporate Integrity Agreement
  - Scope
    - Covered Persons include company personnel involved in contracting with HCPs to conduct clinical trials and other post-marketing studies of products reimbursed under federal healthcare programs (Product Related Functions)
  - Obligations
    - Company must maintain policies and procedures addressing conduct of Product Related Functions in accordance with FDA and federal healthcare program requirements
    - Company must maintain policies addressing ITTs including: (1) decision to provide support for study, (2) manner in which support is provided, (3) support for publication of information about studies, and (4) uses made of information about studies

Compliance Environment: Recent Enforcement Actions

- AstraZeneca CIA Obligations
  - Company training and education must address FDA and federal health care program requirements related to contracting with HCPs to conduct research studies
  - Company subject to Independent Review Organization review which includes Product Related Functions
  - Company must develop monitoring program for non-promotional activities including research-related activities
    - Written agreements describing work, fees, compliance obligations
    - Payment in accordance with centrally managed, pre-set rate structure determined based on fair market value analysis
    - Annual budget plan reviewed by compliance for research-related activities
    - Needs assessment for each researcher engaged
    - Monitoring to ensure research work performed
    - Risk-based audits of research arrangements with results submitted to compliance

Compliance Environment: Recent Enforcement Actions

- AstraZeneca CIA Obligations
  - Public disclosure on website of HCP payments
    - Payments to be disclosed consistent with payments under Section 6002 of Patent Protection and Affordable Care Act
  - Registration of clinical studies on NIH website and posting of results on NIH website and on company website
  - Posting of postmarketing commitments on company website

Compliance Environment: Recent Enforcement Actions

- Physician Researcher (Scott Reuben) (2010)
  - Investigation by DOJ and private pharmaceutical companies
  - Allegations
    - Entered into independent research grant agreements with various pharmaceutical companies to conduct independent clinical research
    - Entered specifically into one independent research grant agreement with a company to conduct independent clinical research and publish the results of the clinical research in a medical journal in exchange for a grant
      - Failed to enroll patients in clinical studies according to the independent research grant agreement
      - Published reports in journals that were fabricated

Compliance Environment: Recent Enforcement Actions

- Scott Reuben Outcome
  - Pled guilty to health care fraud
  - Sentence recommendation
    - Prison/supervised release
    - Restitution to companies ($362,000)
    - Fines/forfeitures/other payments of approximately $55,000

Compliance Environment: Recent Enforcement Actions (Medical Device Insight)

- Synthes (2010)
  - Investigation by DOJ, FDA, and OIG
  - Allegations
    - Company conducted clinical trials of medical device without FDA authorization
      - Studies involved off-label use subject warning on label
  - Settlement
    - Guilty plea (Synthes subsidiary) to one felony count of conspiracy to impair and impede lawful functions of FDA and (Synthes and subsidiary) to misdemeanor counts of shipping adulterated and misbranded device in interstate commerce
    - Upon conviction, potential criminal and civil payments of about $24 million
    - Exclusion for Synthes subsidiary
    - CIA (5 years) with specific obligations addressing research-related activities

Compliance Environment: Recent Enforcement Actions (Medical Device Insight)

- Synthes Corporate Integrity Agreement
  - Scope
    - Covered Persons include company personnel involved in clinical investigations (including personnel with responsibility for clinical investigator financial disclosures)
  - Obligations
    - Company must maintain policies and procedures addressing conduct of covered functions in accordance with FDA and federal healthcare program requirements
    - Company must maintain policies and procedures addressing sponsorship, funding of, and disclosures relating to research and development-related activities
    - Company must conduct specific training and education on clinical investigation compliance
    - Company subject to Independent Review Organization Review for all covered functions

Compliance Environment: Recent Enforcement Actions

- Synthes, Inc. (2009)
  - Investigation by New Jersey Attorney General
  - Allegations
    - Majority of physician investigators for company medical device had investments in device
    - Company failed to disclose financial interests to FDA
      - Financial disclosure forms left blank or interests disclosed without details
  - Settlement
    - Reimbursement of fees and costs related to investigation
    - Voluntary assurances
      - Selection of clinical investigators based on qualifications
      - Fair market value payment not tied to outcome of clinical trial or in form of company stock/stock options

Compliance Environment: Recent Enforcement Actions

- Synthes Settlement
  - Voluntary Assurances
    - Procedures for diligent collection of financial interest information
    - Disclosure of financial interest information to clinical sites and subject and on website (upon product approval/clearance)
- Additional New Jersey Attorney General Action
    - Letter to FDA

Compliance Environment: Government Initiatives

- DOJ
  - Ongoing focus on health care fraud in pharmaceutical industry
    - Payments to researchers often potential issue under consideration
  - Increasing focus on FDA issues
  - Potential new focus on payments to clinical researchers who conduct foreign clinical trials
- OIG
  - Ongoing focus on FDA oversight of clinical trial activities
    - OIG Workplan (2010): FDA Oversight of Investigational New Drug Applications
  - OIG reports identifying concerns
    - FDA Oversight of Clinical Trials (2007)
    - FDA Oversight of Clinical Investigator Financial Information (2009)
    - Challenges to FDA's Ability to Monitor and Inspect Foreign Clinical Trials (2010)

Compliance Environment: Government Initiatives

- FDA
  - Initiatives to enhance oversight and enforcement of sponsor and clinical investigator compliance
    - Increased sponsor responsibilities and increased enforcement
  - Guidance (Examples)
    - Guidance for Industry: Investigation Responsibilities (October 2009)
    - Information Sheet Guidance for IRBs, Clinical Investigations, and Sponsors: FDA Inspections of Clinical Investigations (June, 2010)

Compliance Environment: Government Initiatives

- Proposed Regulations (2010)
  - Sponsors must report information indicating that any person has, or may have, engaged in falsification of data in the course of performing or reviewing clinical trials or reporting study data
  - Report to FDA within 45 days
- Increased Enforcement Action Following Inspections under FDA Bioresearch Monitoring Program
  - Warning letters address sponsor oversight of clinical investigation activity
  - FDA may hold sponsor responsible (additional inspections, warning letter, or rejection of data)
    - Possibility of independent third party audit

Compliance Environment: Government Initiatives

- Disclosure and Transparency
  - Federal
    - Section 6002 of Patent Protection and Affordable Care Act (Physician Payments Sunshine Law Provision)
      - Delayed disclosure for research/clinical trial agreements related to new drug or new application for drug
  - State
    - Number of states require disclosure of payments to HCPs
    - Treatment of research-related payments varies
      - Exemption versus delay versus confidentiality for information submitted
      - Payment of research grant versus payment for research services
      - Pre-approval versus post-marketing clinical trials

Compliance Actions: Key Themes

- Compliance distinction between research arrangements with HCPs and commercial arrangements with HCPs disappearing
  - Standard safeguards for commercial arrangements being imposed on research arrangements
  - Some distinction between pre-approval clinical trials and post-marketing studies remains
    - Status of IITs
  - Need may now exist to justify any differential in compliance treatment
- Government enforcement agencies far along "learning curve" with respect to research-related activities

Compliance Actions: Key Themes

- Illegal remuneration in research context creates multiple concerns = attractive enforcement focus
  - Research payments as mechanism for payment of illegal remuneration
  - Illegal remuneration affect research results (i.e., undermine integrity of clinical trial)
- Research arrangements no longer viewed in isolation
  - Research → publication → dissemination of results
- Enhanced expectations regarding compliance involvement in research arrangements

Compliance Actions: Key Themes

- Disclosure, management or elimination of financial conflict of interests
  - Broad focus on transparency
  - Dual concerns of objective decision-making and research integrity
  - Competing manufacturer concern of confidentiality of proprietary information
- Increased responsibility for research sponsors and increased liability for failure to fulfill responsibilities
  - Clinical trial oversight emerging risk area
- Global focus with foreign clinical trials
  - Foreign Corrupt Practices Act rather than Anti-Kickback Statute

Compliance Actions: Key Steps

- Compare policies and procedures for research arrangements with HCPs and commercial arrangements with HCPs and ensure differences are justified
- Assess funding and oversight of clinical trials (particularly post-marketing clinical trials) based on recent CIA requirements
  - Consider IIT treatment
- Ensure audits/reviews of research arrangements with HCPs are integrated into comprehensive risk-based compliance audits
- Consider compliance audit/review to identify/assess any relationships among research funding, publication funding and dissemination of research results

Compliance Actions: Key Steps

- Assess application of compliance policies to foreign clinical trials and level of oversight
  - Research-related policies
  - Foreign Corrupt Practices Act policies
- Consider whether need to revise clinical trial agreements (CTAs) and enhance site monitoring
  - CTA provisions to ensure investigators are compliant with enhanced/clarified responsibilities and to enhance obligations regarding financial disclosure and overall reporting
- Assess efficacy of financial disclosure mechanisms
  - Review FDA submission
  - Compare information received to other publicly-available information

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