ARNOLD & PORTER LLP

Recent Trends in Corporate Integrity Agreements Affecting Medical Communications and Non-Promotional Activities

Second Annual Q1 Medical Communications Conference (Boston, MA)

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Feb. 22, 2013

Introduction

- Many medical products companies are wrestling with how to impose appropriate controls over medical/scientific activities while still showing value in today's high-pressure marketplace

- Corporate Integrity Agreements (CIAs) are useful in giving us forward-looking information in how compliance and governance infrastructures will be evolving over the next few years

Some Hot Button Issues…

- Proactive vs. reactive communications with customers
- Compliance with FDA draft and final guidance on scientific exchange
- Appropriate role of Health Economics functions
- Rules of engagement between medical/scientific staff and payors
- Safety trending/signal detection and level of disclosure required to patients, HCPs, and payors
- Control over contractors and third parties (CROs, medical communication agencies, reimbursement support services, etc.)
- Control over OUS research activities (and US implications)

BACKGROUND ON CORPORATE INTEGRITY AGREEMENTS

What is a CIA?

- Essentially a contract between a regulated entity and OIG-HHS
  - Not judicially administered or enforceable (unlike a Consent Decree for Permanent Injunction)
  - Condition to continue to do business with the government
  - Generally five-year obligation
- Specific requirements tailored to the entity and the allegedly unlawful conduct
  - Can range from requiring existing procedures to continue, to creating new reporting structures and positions within company
  - Monitoring by Independent Review Organization (IRO)
  - Special terms where OIG-HHS is concerned about quality of patient care (typically healthcare providers)

Relevant Legal Authorities

- CIAs are derived from OIG-HHS's general authority to curb fraud, waste, and abuse but are not creature of statute or regulation
- Imposed upon the resolution of a government investigation into civil misconduct – violations of the federal False Claims Act (FCA)
- Underlying allegations usually implicate other laws:
  - Federal Food, Drug, and Cosmetic Act
  - Federal Anti-Kickback Statute
  - The "Stark" Anti-Referral Laws
  - Federal Price Reporting and Contracting Laws
  - Medicare/Medicaid Fraud Statutes
  - Statutes prohibiting False Statements to regulators

Relevant Legal Authorities (cont'd)

- Increasingly, the US Department of Justice (DOJ) will consider the imposition of a CIA as a factor in filing or deferring criminal charges against medical products companies and providers
  - CIAs often part of the agreed-upon global resolution of civil and criminal investigations
  - Deferred Prosecution Agreements often make explicit reference to the CIA
- The stakes for CIA compliance are therefore very high for companies that have recently resolved allegations of criminal and civil misconduct under federal healthcare laws

Factors OIG-HHS Will Consider

- Did the program participant self-disclose the alleged misconduct?
- What was the monetary damage to Federal health care programs?
- Did the case involve successor liability?
- Is the defendant still a program participant or in the same line of business that gave rise to the conduct?
- Could the unlawful conduct be repeated?
- When did the conduct occur?
- Does the program participant have an effective compliance program?
- Is the program participant willing to enact additional compliance measures and certify compliance?
  - See, e.g., OIG-HHS, Open Letter to Health Care Providers (Nov. 20, 2001)

Elements of an Effective Compliance Program

- Written policies and procedures
- Designation of compliance officers and compliance committee
- Effective training and education
- Effective lines of communication between compliance function and employees
- Enforcement of standards through well-publicized disciplinary guidelines
- Auditing and monitoring
- Responding to detected offenses and taking necessary corrective action
  - See, e.g., OIG-HHS, Compliance Program Guidance for Pharmaceutical Manufacturers (May 2003)

TRENDS AFFECTING MEDICAL COMMUNICATIONS AND OTHER NON-PROMOTIONAL ACTIVITIES

Where We Are Today…

- In the past few years, OIG-HHS has been focusing on previously "untouched" areas such as publication development practices, payor interactions and transparency in research
  - Review of medical/scientific communications has become a standard part of CIAs in off-label cases (e.g., Lilly, Pfizer, Novartis, GSK, many others)
  - Functional heads of Medical Affairs and R&D now being required to sign accountability certifications (e.g., Merck 2011, Amgen 2012)
  - Clinical activities overseas can be swept into US CIA requirements (e.g., GSK 2012)

GSK Settlement (July 2012)*

- Historic $3 billion settlement to resolve criminal and civil liability
  - Settlement resolves a far-reaching investigation into GSK pharmaceutical sales, marketing, and contracting practices regarding numerous drugs including Paxil®, Wellbutrin®, and Avandia®
  - GSK pleaded guilty to three misdemeanor violations of the federal Food, Drug, and Cosmetic Act ("FDCA")
  - Complaints unsealed along with numerous internal GSK documents including emails, sales plans, video recordings of sales meetings, and an HR complaint
- Extensive five-year CIA (including compensation "clawback" provision)

* Because the parties in these cases have not gone to trial, many of the allegations contained in public settlement filings must be regarded as contended facts that have not been proven.

Paxil® Criminal Case

- GSK pleaded guilty to one misdemeanor count of distributing a misbranded drug (Paxil®)
  - Paxil® was approved to treat depression in adults in December 1992 (the drug was subsequently approved for other uses in adults)
  - Theory based on dissemination of false and/or misleading promotional labeling under 21 U.S.C. § 352(a)
- According to the Information, three Paxil® studies were conducted between 1994 and 2001:
  - Study 377 compared the efficacy of Paxil® to placebo in depression patients aged 13-18
  - Study 329 compared use of Paxil® and another anti-depressant (imipramine) against placebo in depression patients aged 12-18
  - Study 702 compared the efficacy of Paxil® to placebo in depression patients aged 7-17
- All three studies allegedly failed on all pre-determined primary and secondary endpoints

Paxil® Criminal Case (cont'd)

- A GSK employee and a contractor allegedly worked together with investigators to write a manuscript of Study 329; the manuscript was published in the American Academy of Child and Adolescent Psychiatry ("JAACAP") in July 2001
  - The manuscript suggested Paxil® was effective based on three secondary endpoints which had not been pre-defined in the study protocol
  - The manuscript did not disclose that Paxil® had failed on all pre-defined endpoints, nor did it note that three endpoints had been added after the study was complete but prior to unblinding
  - The GSK employee asked the contractor rephrase the manuscript section describing 11 adverse events from "worsening depression, emotional ability, headache, and hostility were considered related or possibly related to treatment" to suggest that of the 11 patients "only headache (1 patient) was considered by the treating investigator to be related to" Paxil® treatment

Paxil® Criminal Case (cont'd)

- Subsequent to the JAACAP publication, safety signals led to Paxil® label changes
  - In June 2003, FDA recommended that Paxil® not be used to treat depression in patients under age 18 based on the aforementioned studies and additional statistical analyses performed by GSK, some which linked Paxil® use to increased suicidality risk in adolescents
  - In October 2003, FDA stated that antidepressants should only be used with caution to treat adolescents
  - In October 2004, FDA required all antidepressants to include a black box warning stating that antidepressants increased the risk of suicidal thinking and behavior in patients under age 18

Paxil® Criminal Case (cont'd)

- The contractor allegedly provided copies of the JAACAP article to the head of the Paxil® marketing team
  - Marketing sent the JAACAP article to all 1900 sales reps who carried Paxil® with a cover memo indicating that the article contained study results demonstrating Paxil® efficacy in adolescents
  - The memo did not disclose that Study 329 had failed on all pre-determined endpoints; the memo also did not disclose that Studies 377 and 701 had failed
  - Sales reps subsequently promoted Paxil® for adolescent use using the JAACAP article as well as other off-label materials (such as off-label speaker program slide decks)
- GSK also allegedly used speaker programs, dinner meetings, and other events to promote Paxil® off-label, including by inviting child psychiatrists to speak on off-label uses and paying for attendee travel, meals, and lodging
  - GSK conducted return-on-investment ("ROI") on these events and noted that HCPs who attended generally increased prescribing of Paxil®
  - Despite the negative Paxil® safety signals and label changes, GSK permitted sales reps to provide samples to adolescent psychiatrists until August 2003

Avandia® Criminal Case

- GSK pleaded guilty to one misdemeanor count of failing to report required Avandia® data to FDA
  - GSK was required to provide FDA with periodic reports regarding post-marketing adverse events and annual reports detailing, *inter alia*, the status of and results from ongoing clinical studies (*see* 21 U.S.C. §§ 355(k)(1), e; 21 C.F.R. §§ 314.80, 81)
- The Information charges that between 2001 and 2007, GSK failed to provide FDA with reports for several ongoing studies related to Avandia®, including two studies conducted outside the United States ("Study 211" and the "RECORD Study") at the request of <u>European</u> regulatory authorities
  - The two European studies were conducted specifically to study increases in serious cardiac events associated with Avandia® in patients with weight gain, or on diabetes medications

Amgen Settlement (Dec. 2012)

- Historic $762 million settlement to resolve criminal and civil liability
  - Largest biotech company settlement to date
  - $150 million in penalties and forfeiture; guilty plea for distribution of misbranded Aransep®
  - $612 million to resolve false claims allegations related to alleged off-label promotion, kickback, and fraudulent pricing practices for Aransep®, Embrel®, and Neulasta®
  - Numerous investigating authorities aided by ten whistleblowers
- Five-year CIA has unprecedented detail on expectations for medical/scientific activities, including clinical research conduct, payor and compendia interactions, and publication development and review

Our Focus Today is on Certain Common Themes in the GSK and Amgen CIAs…

Rigorous compliance controls (including monitoring and auditing) to ensure:

- Independence of medical/scientific activities from commercial influence
- Appropriate intersection of Medical Affairs and Health Economics functions in managed care outreach activities
- Legitimacy and transparency of clinical research-related activities
- Appropriate scientific publication planning, review, and support practices
- Adequate safety reporting in clinical research activities

Independence from Commercial

Amgen CIA Section III.B.3.h. (Policies and Procedures)

- "...[T]he manner and circumstances under which Regional Medical Liaisons (RMLs) and other medical personnel within Scientific Affairs and the Global Development Organization interact or participate in meetings or events with HCPs, HCIs, or Payors (either alone or with Amgen sales representatives) and the role of the medical personnel at such meetings or events, as well as how they handle responses to requests for information about off-label uses of Government Reimbursed Products. These Policies and Procedures shall require that RMLs and other medical personnel not engage in the off-label promotion of Government Reimbursed Products…"

Independence from Commercial (cont'd)

GSK CIA Section III.B.3.u. (Policies and Procedures)

- "…GSK represents that it requires Research to be approved by its medical and/or research organization. Under GSK's current policies and procedures, sales, marketing, or other commercial personnel may not participate in the design, conduct, or publication of GSK-Sponsored Research, with limited exceptions relating to non-interventional health outcomes studies (for which a relevant GSK medical group has oversight)…"

GSK CIA Section III.M. ("Monitoring of Non-Promotional Activities")

- "…GSK represents that its commercial organization (including the sales and marketing departments) have no involvement in, or influence over, the review and approval of medical education grants…"

Intersection of Medical Affairs and Health Economics

GSK CIA Section III.B.3.f. (Policies and Procedures)

- "…the materials and information that may be distributed by GSK personnel from the [Policy, Payers, and Vaccines Unit] and the manner in which PPV personnel respond to requests for information about off-label uses of Government Reimbursed Products. These Policies and Procedures shall require that all requests for information about off-label uses…be referred to Medical Affairs (i.e., Medical Information Scientists (MISs), Medical Science Liaisons (MSLs), and/or Health Outcome Liaisons (HOLs))…"

GSK CIA Section III.M. ("Monitoring of Non-Promotional Activities")

- Consultant arrangements, research-related activities, publications, and medical education grants

Intersection of Medical Affairs and Health Economics (cont'd)

Amgen CIA Section III.B.3.s. (Policies and Procedures)

- "…The Global Health Economics organization has a dual reporting line to R&D and commercial, and Research conducted by Global Health Economics is subject to oversight by the R&D organization. The Biosimilars organization also has a dual reporting line to R&D and commercial, and Research conducted by the Biosimilars organization is subject to oversight by the R&D organization."

Intersection of Medical Affairs and Health Economics (cont'd)

GSK CIA Section III.B.3.t. (Policies and Procedures)

- "…the submission of information about any Government Reimbursed Product to any compendia such as Drugdex or other published source of information used in connection with the determination of coverage…includes any initial submission of information…and the submission of any additional, updated, supplemental, or changed information (e.g., changes based on GSK's discovery of scientifically unsound information or data associated with the information in the Compendia)...shall include a requirement that GSK conduct an annual review of all arrangements, processing, fees, or other payments or financial support (if any) provided by GSK to any Compendia…"

Legitimacy of Research-Related Activities

Amgen CIA Section III.B.3.s. (Policies and Procedures)

- "…sponsorship or support by Amgen of post-marketing research involving consented human subjects and Government Reimbursed Products that is conducted by HCPs licensed to practice medicine in the U.S.…[t]his includes post-marketing clinical trials…other post-marketing studies sponsored by Amgen…and support of Amgen of ISSs…"
- "…decision to provide financial or other support…the manner in which Research support is provided; the publication of information about the Research, including publication of information about the Research results and trial outcomes…and uses made of publications…"

Legitimacy of Research-Related Activities (cont'd)

Amgen CIA Section III.B.3.s. (Policies and Procedures)

- "…Amgen represents that it requires all Research sponsored or funded by Amgen [to] address a legitimate scientific question or need, and be reviewed and approved by the relevant governance body within its research and development organization. R&D personnel are responsible for all steps of the design, conduct, and/or publication of the Research. Commercial personnel do not participate in the approval of the publication of Research results…"

Amgen CIA Section III.K. (Monitoring and Auditing)

- Specific monitoring and auditing of researcher arrangements and publication activities to ensure "that these arrangements or activities fulfill legitimate Amgen business or scientific needs."

Legitimacy of Research-Related Activities (cont'd)

GSK CIA Section III.B.3.u. (Policies and Procedures)

- "…GSK also represents that its human subject research and any resulting publications are intended to foster increased understanding of scientific, clinical, or medical issues. To the extent not already accomplished, GSK shall require as a condition of its funding that all researchers disclose in any publication of Research, GSK's support and any financial interest the research may have in GSK…"

Legitimacy of Research-Related Activities (cont'd)

Amgen CIA Section III.K.1.e. (Research Controls)

- All researchers must enter into written agreements describing the scope of work to be performed, the fees to be paid, and the compliance obligations of the Researchers;
- If payment or funding is provided, amounts must reflect fair market value for services rendered;
- Prior to retention of the researcher, Amgen must define the scope of the proposed research and confirm that researchers are appropriately qualified to perform the activities; and
- Amgen must verify that there is a legitimate business or scientific need for the research before payment is made.

Transparency of Research-Related Activities

Amgen CIA Section III.B.3.s. (Policies and Procedures)

- "…Amgen represents that it has established policies, procedures, and practices with respect to prematurely discontinues Amgen-Sponsored Research, which require timely notification of the relevant institutional review board or ethics committee about the decision and reasons for premature discontinuation. As specified in Amgen's Policies and Procedures governing clinical disclosure, Amgen posts status updates with respect to Amgen-Sponsored Research (including discontinued studies) to the NIH-sponsored website (www.clinicaltrials.gov)."

Amgen CIA Section III.N. (Other Transparency/Disclosure Initiatives)

- In addition to compliance with the Sunshine Act and posting on clinicaltrials.gov, Amgen (like GSK) is required to post the results of any post-marketing study commitments on its company website

Scientific Publications

GSK CIA Section III.B.3.u. (Policies and Procedures)

- "…GSK represents that it generally seeks publication of results of all GSK-Sponsored interventional Research in peer-reviewed, searchable journals and imposes specified timeframes for the drafting and submission of manuscripts following completion of a study…"
- "…GSK represents that it has established policies and "operating practices" governing scientific engagement, which included detailed directions regarding publications. Among other things, the operating practices require the implementation of data dissemination plans that establish prospective publication strategies for GSK-sponsored research and address requirements for appropriateness, accuracy, and balance…"

Scientific Publications (cont'd)

Amgen CIA (Section III.B.3.u.) (Policies and Procedures)

- "While recognizing the decision-making role of the authors and journals, respectively, Amgen represents that it makes good faith efforts to publish Amgen-Sponsored Research results in peer-reviewed journals and includes specified timeframes for the submission of manuscripts following completion of an Amgen-Sponsored Research study in the global publication plan for each Government Reimbursed Product…Amgen further represents that its written agreements pertaining to ISSs require the investigator to exercise best efforts to publish the results of the ISS."

Safety Reporting in Clinical Research

GSK CIA Section III.B.3.u. (Policies and Procedures)

- "GSK represents that it has established policies, systems, and practices designed to ensure that adverse event data is properly reported to the FDA. In addition, GSK requires investigators to report study-related information and data, including data about adverse events before receiving final payment from GSK."

Safety Reporting in Clinical Research (cont'd)

Amgen CIA Section III.B.3.u. (Policies and Procedures)

- "Amgen represents that it has established policies, systems, and practices designed to ensure that adverse event data is collected, processed, analyzed, communicated, and reported to FDA. Amgen requires sponsors of ISSs to agree to provide Amgen with safety reports as a condition to providing support for ISSs, and during the study, Amgen assesses the sponsor's compliance with safety reporting requirements per contractual agreements…"

Questions?

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