Corporate Integrity Agreements 2012

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Abstract

Objective: US Department of Health & Human Services (HHS) Office of the Inspector General (OIG) works with the Department of Justice (DOJ) investigating alleged Medicare and Medicaid service provider misconduct, imposing fines and issuing Corporate Integrity Agreements (CIAs) to pharmaceutical companies. We examined CIAs issued in 2012 with provisions specific to publications related activities.

Research Design and Methods: Previous year public records of OIG and DOJ pertaining to pharmaceutical company CIAs were reviewed.

Results: Four CIAs met criteria. General provisions of the CIAs are similar to those previous: strict authorship criteria, written authorship agreements, disclosure of funding/sponsorship, and needs assessment. Two CIAs went beyond this. Allegations of off-label promotion for one company specified years of dissemination of inaccurate and misleading publications and downplaying safety data, before eventually admitting no evidence of drug benefit. The CIA required future publications not downplay safety, and be balanced and timely. In another, specifications alleged improper conduct in manuscript development and submission, response to reviewer comments, and subsequent resubmission and publication that misrepresented clinical significance and product safety. The CIA required appropriateness, accuracy, and balance in presentation of clinical study results in future publications and educational activities.

Conclusions: DOJ and OIG continue to scrutinize publication activity and include publication-related sanctions in their 2012 CIAs. Two followed investigations that reviewed published articles for accuracy and appropriateness of content. They focus on important components of good publications practices beyond process, i.e. publications are responsible and timely, in accordance with established reporting standards.

Objective

Office of Inspector General (OIG) conducts investigations
- Civil and criminal
- Of fraud and misconduct
- Related to Health and Human Services (HHS) programs or their beneficiaries
- Including State False Claims Act reviews

OIG negotiates corporate integrity agreements (CIA) with health care providers and entities
- Under a variety of civil false claims statutes
- Providers or entities agree to certain obligations
- OIG agrees not to exclude providers or entities from Federal health care programs

Department of Justice (DOJ) conducts criminal health care fraud investigations
- Under statutory provisions of the Health Insurance Portability and Accountability Act of 1966 (HIPPA)
- The Health Care Fraud and Abuse Control Program
- Coordinates Federal, State, and local enforcement efforts
- Relating to the delivery of and payment for health care in the United States

Methodology

Internet search of OIG and DOJ web sites
- Identified OIG pharmaceutical companies CIAs
- Dated between January 1 and December 31, 2012
- Identified associated DOJ press releases
- Located and downloaded DOJ supplemental documents on criminal investigations for the pharmaceutical companies CIA
- To include "Agreed Statements of Facts" and "United States Complaint"
- Read CIAs, press releases, and available court documents

Results

Four CIAs were identified in 2012; a similar study done last year identified 10 CIAs between 2007 and 2011
- CIA provisions for 2007–2011 focused on the ***process*** of developing publications
- CIA provisions in 2012 also addressed ***process*** but we see expansion into publications ***content***
- The table below summarizes basic ***process*** issues in the CIAs

Table 1.

	2007	2009	2010					2011			2012			
CIA Provisions regarding PROCESS	MED	PFZ	AZN	OMJ	AGN	FST	NOV	UCB	NND	MRK	ABB	GSK	AMG	BIP
Publications are:														
"Promotional and product related functions"				x				x						
"Product related functions "					x	x	x		x	x	x	x	x	x
"Non-Promotional activities			x		x	x	x	x		x	x	x	x	x
Authors:														
Written agreement		x	x		x	x	x	x		x	x	x	x	x
Meet ICMJE criteria		x	x		x	x	x			x	x	x	x	x
Payments at fair market value		x	x		x	x	x	x			x	■	■	x
Disclosure of relationship to company, financial support		x	x		x	x	x	x		x	x	x	x	x
Disclose writing/ editorial support		x	x	x	x	x	x	x		x	x	x	x	x
Scope/breadth of data to authors			x		x	x	x	x		x	x	x	x	x
Planning:														
Needs assessment		x	x		x	x	x	x		x	x	x		x
Needs assessment approved by legal department		x												
Needs assessment approved by compliance			x		x	x	x	x		x	x	x		x
Publications Plan approved by compliance			x		x	x	x	x			x	x		x
Policies/Procedures:														
Address authorship	x		x	x	x	x	x	x		x	x	x	x	x
Address publications				x		x	x	x		x	x	x	x	x
Publications monitoring		x	x		x	x	x	x		x	x	x	x	x
Compliance Officer/program	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Abbreviations: MED=Medicis; PFZ=Pfizer; AZN=AstraZeneca; OMJ=Ortho-McNeil-Janssen; AGN=Allergan; FST=Forest; NOV=Novartis; UCB=UCB; NND=Novo Nordisk; MRK=Merck; ABB=Abbott; GSK=GlaxoSmithKline; AMG=Amgen; BIP=Boehringer Ingelheim Pharmaceuticals

■ = no payment permitted for writing/authorship

Publications Content in CIAs

- ***Content*** in 2007–2011: Was there a need? Were authors provided data?
- ***Content*** in 2012: Was there a need? Were authors provided data? PLUS *was it balanced? Accurate? Exaggerated? Appropriate?*

2012 CIAs

- Two of the CIAs had provisions consistent with those previously reported:
  - The Boehringer Ingelheim CIA had few comments on publications activity, but all dealt with process
  - The GSK and Amgen CIAs added a provision regarding payment to authors:
    - *With certain limited exceptions, no compensation is paid to Authors for their time spent drafting or revising Publications* (Amgen CIA p. 36)
- For these CIAs, any criminal allegations remain under seal
- For the other 2 CIAs, the criminal cases are not under seal:
  - Providing insight regarding CIA content provisions

Table 2.
ABBOTT LABORATORIES
Criminal Case #1.12CR26
Agreed Statements of Fact, May 7, 2012

Divalproex	**Mania in Dementia**
Study M97-738	• FDA expressed reservations about a new or expanded use of divalproex for mania • Study was suspended because of increased incidence of adverse events – somnolence and thrombocytopenia – dose too high • Results failed to show efficacy in treating signs/symptoms of mania in dementia • Only one secondary measurements showed positive results • Clinical study report concluded this positive result was independent of somnolence • Changed objectives in subsequent trial to target agitation instead of mania
	Published in *Current Therapeutic Research* in 2001 • ". . .did not improve signs and symptoms of mania associated with dementia . . . but did improve symptoms of agitation."
Divalproex	**Agitation in Dementia**
Study M99-082	• Study called for lower dosage • Terminated trial for low enrollment • Failed to separate from placebo • CSR reported 2 divalproex groups and placebo group all showed improvement on all primary and secondary measures
	Results not published or disseminated except to FDA
"Rochester" study *Partially funded by Abbott*	• First phase "suggest[ed], but did not prove" divalproex improved agitation in dementia in spite of no difference vs. placebo
	First published in *American Journal of Psychiatry* in 2001 • 68% of divalproex, 52% of placebo subjects with reduced agitation
	Second part of study published in *The American Journal of Geriatric Psychiatry* in 2003 • "suggested but did not prove" that "therapy can result in decreased measures of agitation"
"ACDS Study" *National Institute on Aging funded, Abbott supplied drug product*	• No benefit over placebo
	Published in *American Journal of Geriatric Psychiatry* in 2005 • Advanced copy to Abbott December 2004 • No evidence that divalproex was meaningfully different than placebo • Abbott continued to distribute "Rochester" study 2003 article until 2006
Divalproex	**Augmentation in Acute Exacerbation of Schizophrenia**
Study M99-010	• Divalproex in combination with atypical antipsychotic (ATP) • Per FDA Abbott failed to meet predefined endpoint [significant improvement at 28 days compared to ATP alone] – and did not support application for new indication
	Published in *Neuropsychopharmacology* in 2003 • Stated combination therapy showed significant improvement day 3 through day 21 downplaying failure to meet primary endpoint of day 28 • Findings "confirmed in post hoc repeated-measures analysis of variance"
Study N02-547	• Did not show any significant treatment difference between combination therapy and ATP alone
	Published in *Neuropsychopharmacology* in 2008 • No significant treatment difference

Table 3.
GLAXOSMITHKLINE
Criminal Case #11-10398-RWZ
United States Complaint, October 26, 2011

Paroxetine	**Efficacy for Depression in Children and Adolescents**
Study 329	• Study ran from 1994–1998 • Failed to demonstrate efficacy on the two primary and five secondary predefined variables – Several additional secondary measures added – Separated from placebo on some of these
	Submitted to *JAMA* in 1999 • As "safe and effective treatment for major depression in adolescents" • Reviewer comments critical – That treatment effect not much different than placebo – "numerically superior" used for non-significant differences Resubmitted to *Journal of the American Academy of Child and Adolescent Psychiatry* in 2000 • Reviewer comments critical – Results do not demonstrate efficacy – No a priori primary outcome measure reported Comments not addressed and published in 2001 • Primary endpoints identified in abstract but article did not state failure to show superiority to placebo • Falsely stated paroxetine separated from placebo on "response" when "response" was one of the predefined primary endpoints • Separated from placebo on 3 of 5 secondary measures, misleading by calling these a priori when they were not protocol-defined
Study 377 and Study 701	• 1995–1998 and 2000–2001 • Neither study demonstrated efficacy
	Results not published
Paroxetine	**Safety for Depression in Children and Adolescents**
Study 329	• Reviewer for *JAMA* submission in 1999 – MS did not note that paroxetine had significantly more serious adverse events than placebo (and imipramine) • 5 events labeled as "emotional lability" were "suicidal ideation/gestures, overdoses" • FDA identified 5 additional events as possibly suicide-related • Of 11 serious adverse events reported, only 1 was considered "related" – Events considered "possibly related" were treated as "unrelated" – 5 required hospital admission and were events with known association with SSRIs
	Published in *Journal of the American Academy of Child and Adolescent Psychiatry* in 2000 • As generally well tolerated • Regarding serious adverse events: "Of the 11 patients, only headache (one patient) was considered by the treating investigator to be related to paroxetine treatment."

Abbott CIA
May 7, 2012

*". . . shall require that scientific publications be published in a timely manner and **present scientific information in a balanced way** that does not exclude or inappropriately downplay negative safety or health information."* (p. 36)

*"Abbott's U.S. compliance personnel shall be involved in the review and approval of such annual Publications Plans, including any modification of an approved plan. The purpose of this review shall be to ensure that Publication Activities and related events are **used for legitimate purposes** in accordance with Abbott Policies and Procedures."* (p. 36)

GlaxoSmithKline CIA
June 28, 2012

*"GSK also represents that its human subject research and any resulting publications **are intended to foster increased understanding of scientific, clinical or medical issues**"* (p. 19)

*". . . 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** in publications of GSK-Sponsored Research."* (p. 20)

Conclusions

We may consider certain types of communication to be *safe harbors*, protected, peer-to-peer scientific communications
- The DOJ criminal investigations have examined the scientific merit of journal article content
- The DOJ cited FDA comments regarding clinical study reports
- The DOJ cited FDA review of adverse events
- The DOJ has cited peer reviewer comments to manuscripts submitted for peer review
- While the articles in question may have also been distributed inappropriately, the criminal complaint discusses article content separately from distribution

The CIAs use terms like *appropriateness, accuracy, balance, legitimate purposes* as requirements for the publications
- This is consistent with GPP2 section on *Reporting standards*
- Nonadherence to reporting standards may risk loss of safe-harbor status

References Cited

Corporate Integrity Agreement Between the Office of the Inspector General of the Department of Health and Human Services and Abbott Laboratories, May 7, 2012, accessed online at https://oig.hhs.gov/fraud/cia/agreements/Abbott_Laboratories_05072012.pdf, March 12, 2013.

Corporate Integrity Agreement Between the Office of the Inspector General of the Department of Health and Human Services and Amgen Inc., December 14. 2012, accessed online at https://oig.hhs.gov/fraud/cia/agreements/Amgen_12142012.pdf, March 12, 2013

Corporate Integrity Agreement Between the Office of the Inspector General of the Department of Health and Human Services and Boehringer Ingelheim Pharmaceuticals, Inc., October 22. 2012, accessed online at https://oig.hhs.gov/fraud/cia/agreements/Boehringer_Ingelheim_Pharmaceuticals_10222012.pdf, March 12, 2013.

Corporate Integrity Agreement Between the Office of the Inspector General of the Department of Health and Human Services and GlaxoSmithKline LLC, October 22. 2012, accessed online at http://www.justice.gov/opa/documents/gsk/plea-ex-d.pdf, March 12, 2013.

United States v. Abbott Laboratories, 2012, Case 1:12-CR-00026-SGW, Document 5-2, Agreed Statement of Facts, accessed online at http://www.justice.gov/opa/abbott-court-docs-2012/StatementofFacts.pdf, March 12, 2013.

United States ex rel, Greg Thorpe, et al. [Consolidated] Plaintiffs v GlaxoSmithKline PLC, and GlaxoSmithKline LLC, Defendants, 2012, C.A. No. 11-10398-RWZ, United States Complaint, accessed online at http://www.justice.gov/opa/documents/gsk/us-complaint.pdf, March 12, 2013.

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