The Relationship Between Overall Utilization And Settlements Involving Off-Label Promotion Of Prescription Drugs

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In acknowledging the support of the individuals and entities recognized above, I do not transfer responsibility for the contents of this dissertation to them. The author remains solely responsible for this work.

Dedication

This dissertation is dedicated to my Mom and Dad, John and Susan Bilek.

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CHAPTER 1
INTRODUCTION

1.1 Introduction

Prescription drug spending has risen over the past two decades. Outpatient spending in the US for prescription drugs was $234.1 billion in 2008, nearly 6 times the $40.3 billion spent in 1990.[1] From 1998 to 2008, prescription drugs contributed 13% of the total growth in national health expenditures, compared to 30% for hospital care and 21% for physician and clinical services.[2]

Given these rising costs, regulators began to turn their attention to fraudulent activity that leads to prescription drug spending by taxpayer funded health care programs. Legislators passed laws and regulations and the Department of Justice began to enforce them in an attempt to curb fraudulent activity that leads to greater dollar amounts spent on prescription drugs. The fraudulent activity that is the focus of this dissertation relates to promotional or marketing tactics employed by pharmaceutical companies to encourage drug sales.

In 2000, pharmaceutical companies spent more than $15.7 billion on promoting prescription drugs in the United States.[3] Pharmaceutical companies spent more than $4.8

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[1] Kaiser Family Foundation, Prescription Drug Trends May 2010. This number reflects current amounts and is not adjusted for inflation.
[2] Centers for Medicare & Medicaid Services, National Health Expenditure Accounts, Historical, http://www.cms.gov/NationalHealthExpendData/ accessed October 6, 2009.
[3] Rosenthal MB, Berndt ER, Donohue JM, Epstein AM, Frank RG (2003) Demand effects of recent changes in prescription drug promotion. Henry J Kaiser Family Foundation. Available: http://www.kff.org/rxdrugs/6085-index.cfm. Accessed March 23, 2007.

billion on detailing, the one-on-one promotion of drugs to doctors by pharmaceutical sales representatives, commonly called drug representatives. The sales force expenditure for pharmaceutical companies was $875 million annually by 2004.[4]

Although pharmaceutical companies commonly market and promote their prescription drugs, the government frowns upon certain types of marketing and promotion. For example, pharmaceutical companies have paid billion dollar settlement amounts to the government based on allegations that the company promoted a drug for uses not approved by the Food and Drug Administration. The Health Care Fraud & Abuse Control Program (HCFAC) account has returned over $15.6 billion to the Medicare Trust Fund between 1997 and 2009.[5] During FY 2009, the Federal Government won or negotiated approximately $1.63 billion in judgments and settlements,[6] and in FY 2011, the Federal government awards reached $2.4 billion.[7] The Justice Department has used the False Claims Act to recover approximately $2.2 billion since January 2009 in cases involving fraud against federal health care programs.[8] A large portion of the recoveries involved pharmaceuticals.

[4] Niles S (2005) Sales force effectiveness (the third in a series of articles that examine problems and solutions of detailing to physicians). 24 Med Ad News 1.
[5] The Department of Health and Human Services and Department of Justice, Health Care Fraud and Abuse Control Program Annual Report for Fiscal Year 2009 (May 2010).
[6] This number reflects Federal recoveries only.
[7] The Department of Health and Human Services and Department of Justice, Health Care Fraud and Abuse Control Program Annual Report for Fiscal Year 2011 (May 2012).
[8] Press Release, Two Johnson & Johnson Subsidiaries to Pay Over $81 Million to Resolve Allegations of Off-label Promotion of Topamax, Department of Justice (Apr. 29, 2010).

1.2 Background and Significance

In testimony given to the members of the Committee on Oversight and Government Reform United States House of Representatives in 2006, the Associate Attorney General, Ronald Tenpas, stated that drug company violations of the law were causing government healthcare programs to pay too much for prescription drugs.[9] These comments are particularly telling because prescription drug spending by government healthcare programs increases every year. With the implementation of Medicare Part D in 2006 as part of the Medicare Modernization Act of 2003[10], the government expanded drug coverage to millions of seniors, and consequently, the amount spent by the government using funding from taxpayers increased.

Even before Medicare Part D went into effect, outpatient prescription drug spending had grown faster than health care spending overall.[11] In 1996, the total retail prescription sales in the U.S. were about $72 billion and by 2006 the sales number increased to nearly $250 billion.[12] The total number of outpatient prescriptions grew from 2.2 billion in 1996 to 3.4 billion in 2006.[13]

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[9] RJ Tenpas, Testimony to Committee on Oversight and Government Reform United States House of Representatives, *Allegations of Waste, Fraud, and Abuse in Pharmaceutical Pricing: Financial Impacts on Federal Health Programs and the Federal Taxpayer*, Associate Attorney General U.S. Department of Justice (February 9, 2007).

[10] The Medicare Prescription Drug, Improvement and Modernization Act of 2003 amended Title XVIII of the Social Security Act. *See* 42 U.S.C. § 1395w-101. Medicare Part D became available in January 2006. 42 U.S.C. § 1395w-101(a)(2).

[11] U.S. DHHS, Office of the Actuary, National Health Accounts, 2004 version, released January 2006.

[12] IMS Health data as reported by the National Association of Chain Drug Stores, (May 7, 2007) http://www.nacds.org/wmspage.cfm?parm1=507. Total retail sales as defined by IMS Health includes outpatient prescription sales of independent pharmacies,

Health care fraud recoveries have been increasing over the last few years. The Justice Department recovered $ 2.4 billion in false claims cases in 2009, which brings the total to $ 24 billion in civil liability recoveries since 1986.[14] Between January 2009 and May 2010, the Justice Department's total recovery in False Claims Act (FCA) cases was an unprecedented $ 3 billion.[15]

1.3 Problem Statement

Given the total dollars spent on prescription drugs, fraudulent activity occurring within the drug industry has major financial implications for government programs that pay for prescription drugs. Ultimately, this financial burden falls to the taxpayers of the United States through increased taxes, increased health insurance premiums, and increased deductibles and/or co-payments. Providing a sample of the scope and scale of particular type(s) of alleged violations of health care laws by pharmaceutical companies may shed light on potential flaws in deterring future violations.

When explaining health care fraud within the pharmaceutical marketplace to the congressional committee in 2006, the Associate Deputy Attorney General, Ronald

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traditional chain pharmacies, supermarket pharmacies, mass merchandiser pharmacies, and mail order pharmacies.

[13] *Id*.

[14] PR Newswire, United Business Media, Justice Department Recovers $2.4 Billion in False Claims Cases in Fiscal Year 2009; More Than $24 Billion Since 1986 (2009), http://www.prnewswire.com/news-releases/justice-department-recovers-24-billion-in-false-claims-cases-in-fiscal-year-2009-more-than-24-billion-since-1986-70521362.html (criminal fines associated with the settlements or verdicts were not included in the Justice Department's tally).

[15] Press Release, Department of Justice Office of Public Affairs, Novartis Vaccines & Diagnostics to Pay More Than $72 Million to Resolve False Claims Act Allegations Concerning TOBI (May 4, 2010).

Tenpas, said, "[w]e are not seeing isolated instances of misconduct, but repeated practices within the industry that have resulted in significant losses to Federal health care programs, including Medicare, Medicaid and the Federal Employees Health Benefits Program, among others."[16] If a company can make more money by breaking the law, and then paying fines if caught; setting aside the arguments regarding patient safety, why not break the law, pay the fines, and still generate more profits?

Secondarily, the study will analyze whether utilization and dollars spent by States and the federal government on Medicaid prescriptions has any influence on settlement amounts. And finally, the study will analyze whether other variables, such as the therapeutic class of the drug(s) involved, overall U.S. dollars spent on the particular drug(s), proportion of utilization allocated to off-label or non-evidence based uses, or FDA Warning Letters are associated with settlement amounts.

1.4 Purpose of Study

The overall goal of this study is to provide a detailed analysis of the scale and scope of allegations involving illegal marketing and promotion of pharmaceutical products brought by the U.S. government to recover money spent on pharmaceutical products via Medicaid due to alleged activity that violates one or more federal laws related to health care fraud. This goal requires an understanding of the intermingling

[16] RJ Tenpas, Testimony to Committee on Oversight and Government Reform United States House of Representatives, *Allegations of Waste, Fraud, and Abuse in Pharmaceutical Pricing: Financial Impacts on Federal Health Programs and the Federal Taxpayer*, Associate Attorney General U.S. Department of Justice (February 9, 2007).

factors that influence the pharmaceutical marketplace, including the laws and regulations that govern the industry.

1.5 Research Objectives and Hypotheses

The study describes, within the context of an in-depth critical read, factors presumed to be relevant to settlement amounts. The primary hypothesis is that settlement amounts are not large enough and do not result in enough consequences to deter the same or other companies from engaging in similar illegal activities.

To my knowledge, no comparison between settlement or verdict amounts and each of the variables studied exists publicly. This study provides a needed framework for policy makers in dealing with an aspect of our growing health care expenditures. The study may also provide a framework for negotiations that could benefit both prosecutors and pharmaceutical companies.

Research Question 1.5.1

What are the trends and association between federal health care fraud and abuse settlement amounts, the total U.S. dollar sales of the pharmaceutical product(s) involved, and the total dollar amount spent by Medicaid for the particular drug(s) within the pre-settlement timeframe?

Objective 1.5.1

Examine how the settlement amounts compare to the amount spent on the drug(s) (1) overall in the retail marketplace and (2) by the government for Medicaid for the particular drugs during the pre-settlement timeframe.

Source

a. The source of U.S. manufacturer dollar sales for dosage units sold per product per month at the manufacturer level was IMS Health National Sales Perspective data.

b. The prescription utilization totals from Medicaid were collected from the Center for Medicare and Medicaid Services (CMS). The total dollar amounts spent on prescriptions paid through Medicaid for the drugs identified in the lawsuit were also obtained from CMS. The CMS database provides state-by-state data. Medicare Part A, B and D prescription drug utilization data was not used. Most of the drugs analyzed were available in the retail pharmacy sector and are not administered solely in a doctor's office or hospital setting where Medicare Part A and B may cover some or all of the costs.

Research Question 1.5.2

What are the trends and association between federal health care fraud and abuse settlement amounts, the total retail utilization of the pharmaceutical product(s) involved (measured in units), and the total utilization by Medicaid for the particular drug(s) (measured in units) within the pre-settlement timeframe?

Objective 1.5.2

Examine how the settlement amounts compare to the utilization of the drug(s) (1) overall in the retail marketplace and (2) by the government for Medicaid for the particular drugs during the pre-settlement timeframe.

Source

a. The source of U.S. manufacturer utilization per product per month (measured in units) at the manufacturer level was IMS Health National Sales Perspective data.

b. The prescription utilization totals from Medicaid were collected from the Center for Medicare and Medicaid Services (CMS). The CMS database provides state-by-state data. Medicare Part A, B and D prescription drug utilization was not used. Most of the drugs analyzed were available in the retail pharmacy sector and are not administered solely in a doctor's office or hospital setting where Medicare Part A and B may cover some or all of the costs.

Research Question 1.5.3

What are the trends and association between the quantity of FDA warning letters, the existence of a black box warning, or the existence of a black box warning related to an off-label use allegedly promoted by the respective company and the settlement amounts?

Objective 1.5.3

Determine whether there is an association between the quantity of warning letters, the existence of a black box warning, or the existence of a black box warning related to an off-label use allegedly promoted by the respective company and settlement amounts.

Source

a. The FDA's website identifies warning letters by year and makes them available on its website. Warning letters alleging activities either related to the lawsuit or unrelated but involving each drug were collected, including the quantity of warning letters per company and per drug.
b. The FDA's website provides access to the package insert or labeling information for most drugs. The latest package insert available as of 2010 was used to identify whether the labeling included a black box warning. A comparison of the specific language of the black box warning and the alleged off-label promotional uses provided the source for results on whether the black box warning related to an off-label use allegedly promoted by the respective company.

Research Question 1.5.4

What are the trends and association between settlement amounts and the ratio of off-label uses relative to all uses for which prescribers prescribed the drug?

Objective 1.5.4

Determine whether settlement amounts are associated with the number or amount of off-label prescribing.

Source

a. The prescribing data for each drug was collected using IMS National Disease Therapeutic Index (NDTI) data and compared against the indications for each drug as listed in the American Hospital Formulary Systems.

Research Question 1.5.5

What are the trends and association between settlement amounts and the ratio between non-evidence based uses relative to the total number of uses for which prescribers prescribed the drug?

Objective 1.5.5

Determine whether the settlement amounts are associated with the number or amount of non-evidence based uses compared to all uses.

Source

a. The prescribing data for each drug was collected using IMS National Disease Therapeutic Index (NDTI) data and compared against the clinical use descriptions for each drug listed in the American Hospital Formulary Systems.

Research Question 1.5.6

What are the trends and association between federal health care fraud and abuse settlement amounts and the total dollars spent on promoting the pharmaceutical product(s) prior to settlement?

Objective 1.5.6

Examine how the settlement amounts compare to the amount spent on promotion for each drug.

Source

a. The source of total dollar spent on promotion was the IMS Health Integrated Promotional Services database.

Research Question 1.5.7

What are the trends and association between settlement amounts and U.S. total dollars and Medicaid dollars allocated to proportion of off-label uses and non-evidence based uses?

Objective 1.5.7

Examine how the settlement amounts compare to dollars allocated to off-label uses and non-evidence based uses.

Source

a. The prescribing data for each drug was collected using IMS National Disease Therapeutic Index (NDTI) data and compared against the clinical use descriptions for each drug listed in the American Hospital Formulary Systems.
b. The source of U.S. manufacturer dollar sales for dosage units sold per product per month at the manufacturer level was IMS Health National Sales Perspective data.
c. The prescription utilization totals from Medicaid were collected from the Center for Medicare and Medicaid Services (CMS). The total dollar amounts spent on prescriptions paid through Medicaid for the drugs identified in the lawsuit were also obtained from CMS. The CMS database provides state-by-state data. Medicare Part A, B and C prescription drug utilization was not

used. Most of the drugs analyzed were available in the retail pharmacy sector and are not administered solely in a doctor's office or hospital setting where Medicare Part A and B may cover some or all of the costs.

Research Question 1.5.8

What are the trends and association between settlement amounts and U.S. total units and Medicaid units allocated to off-label uses and non-evidence based uses?

Objective 1.5.8

Examine how the settlement amounts compare to utilization (measured in units) allocated to off-label uses and non-evidence based uses.

Source

a. The prescribing data for each drug was collected using IMS National Disease Therapeutic Index (NDTI) data and compared against the clinical uses for each drug listed in the American Hospital Formulary Systems.
b. The source of U.S. manufacturer units sold per product per month at the manufacturer level was IMS Health National Sales Perspective data.
c. The prescription utilization totals from Medicaid were collected from the Center for Medicare and Medicaid Services (CMS).

1.6 Implications of the Study

Legislative measures currently in place may not adequately prevent fraudulent activity and the settlement or verdict amounts paid by pharmaceutical companies as a result of allegations of illegal promotion may not provide a reasonable recovery for the

monies lost by the government due to the alleged fraudulent activity. Identifying trends and associations between drug agents, pharmaceutical companies, the specific allegations, and settlement amounts, among other factors, may assist policymakers in understanding and framing amendments to existing legislation.

The study may also assist the government in developing damage models to ensure the full recovery of funds obtained through illegal activities by companies, and at the same time, deter future misconduct. The identification of trends and associations could assist both government and pharmaceutical companies. .

The observations may assist pharmaceutical companies in negotiating settlements by comparing the settlement amount and circumstances present in previous lawsuits to the present situation. In the event the government or qui tam Plaintiff alleges off-label wrongdoing, the observations could assist companies in negotiating with the government rather than spending millions of dollars in litigation expenses. The observations may also assist corporate compliance officers.

CHAPTER 2
BACKGROUND AND LITERATURE REVIEW

Chapter 2 includes four main sections. The first section describes the process used to bring a health care fraud case against a pharmaceutical company. The second section describes the primary laws used to prosecute pharmaceutical companies for promotional schemes, including a brief history of the FDA's position on off-label promotion. The third section describes the tools used to recover health care dollars spent on prescription drugs, and the traditional use of said tools, including a history of how the government has employed these tools to combat health care fraud allegations against pharmaceutical companies. The fourth section describes key literature discussing off-label promotion.

2.1 The Process

The Health Insurance Portability and Accountability Act of 1996 (HIPAA) established a national Health Care Fraud and Abuse Control Program (HCFAC or the Program) under the joint direction of the Attorney General, and the Secretary of the Department of Health and Human Services (HHS).[17] Both the Attorney General and Secretary act through the Department's Inspector General (HHS/OIG).[18] The intent of the Program was to coordinate federal, state, and local law enforcement activities with

[17] HHS & U.S. DEP'T OF JUSTICE (DOJ), HEALTH CARE FRAUD AND ABUSE CONTROL PROGRAM ANNUAL REPORT FOR FY 1998 (1998), available at http://www.usdoj.gov/dag/pubdoc/98hipaa_ar.htm#a (stating that the Health Care Fraud and Abuse Control Program is a far-reaching program to combat fraud and abuse in health care, including both public and private health plans).
[18] *Id.*

respect to health care fraud and abuse.[19] According to the HCFAC Program Annual Report, the 1996 legislation made available "much needed and powerful criminal and civil enforcement tools and financial resources that permitted the government to expand and intensify the fight against health care fraud."[20]

There are two main ways that the government discovers a potentially fraudulent scheme by a provider of health care products and services such as a pharmaceutical company. The first is through one or more whistleblowers that bring cases to the government's attention. Whistleblowers are often former or current employees of the respective entity. When a whistleblower brings a case on behalf of the government, the government can choose to intervene or decline to intervene. In either case, the attorney representing the whistleblower continues to litigate the case with or without the assistance of the government. The False Claims Act (FCA) includes a *qui tam* provision that provides for large recoveries to individuals who bring fraudulent activities to the government's attention. The whistleblower receives about 15% to 30% of the government's recovery if the allegations lead to a settlement or jury verdict.

Whistleblowers account for a large portion of the health care fraud cases brought by the government. For instance, of the $2 billion recovered in the 2007 fiscal year behind allegations of health fraud against the federal government, $1.45 billion was associated with suits initiated by whistleblowers under the FCA's *qui tam* provisions.[21] Of the $2.4 billion recovered in fiscal year 2009, $2 billion was associated with suits

[19] *Id.*
[20] *Id.*
[21] *Id.*

initiated by whistleblowers under the FCA's *qui tam* provisions.[22] The potential for large dollar recoveries for reporting fraudulent activity provides a tremendous incentive to report abuse. The second way that the government discovers a potential scheme is through investigations because of tips from the media, competitors, regulators, consumers, or patients.

After the government receives a tip or agrees to investigate a matter brought by a whistleblower, the government begins with an investigation usually led by the Office of the Inspector General. Once they believe they have enough information the Department of Justice or a state's Attorney General will decide whether to file a lawsuit. In many cases, the attorney(s) who represent the whistleblower will already have filed the lawsuit, and at that point, the government simply intervenes. During the timeframe from initiation of the lawsuit to settlement or final verdict, attorneys for both sides request documents, and both the prosecuting attorneys (i.e. government) and the defense counsel devise their theory of the case and work to develop this theory through fact and expert discovery. At any time in the process, the two sides may decide that they are interested in settling the case rather than going to trial. Most health care fraud cases involving prescription drugs never reach a judge or a jury; most cases are resolved with out of court settlements.

[22] PR Newswire, United Business Media, Justice Department Recovers $2.4 Billion in False Claims Cases in Fiscal Year 2009; More Than $24 Billion Since 1986 (2009), http://www.prnewswire.com/news-releases/justice-department-recovers-24-billion-in-false-claims-cases-in-fiscal-year-2009-more-than-24-billion-since-1986-70521362.html (criminal fines associated with the settlements or verdicts were not included in the Justice Department's tally).

2.2 Regulators, Programs, and Laws

2.2.1 The Food and Drug Administration

The Food and Drug Administration (FDA) regulates drug distribution in interstate commerce. In the pharmaceutical industry, regulation begins with the FDA's drug approval process. The FDA reviews the safety and effectiveness of prescription drugs before granting the company the right to sell and market the drug in the United States. The pharmaceutical company must submit extensive in vitro, animal, and human study data before approval. The FDA must also review and approve the package insert. The package insert is an important aspect of the approval process because it provides detailed information based on observations from the clinical trials submitted by the drug company. The FDA reviews the clinical trial methods and results to determine whether to approve the drug for use in the U.S. marketplace based on efficacy and safety parameters. The FDA must also approve the package insert. The package insert provides information relating to: indications for use, pregnancy risk factor, contraindications, warnings/precautions, common adverse reactions, drug interactions, mechanism of action, pharmacodynamics/kinetics, dosage, administration instructions, monitoring parameters, patient information, and other information.

The FDA approves the indications listed in the package insert based on the data provided by the pharmaceutical company. One of the main allegations the federal government uses when filing lawsuits against pharmaceutical companies involves off-label promotional schemes, which involves promotion of uses not included in the

package insert. Off-label use means using the drug for a condition or disease state not studied or for a use studied but where there is inadequate evidence of efficacy or safety data. Recall, the FDA must approve the label, and approval will not occur until the FDA is satisfied that the label only corresponds to the approved uses.[23] In other words, the term off-label means that the drug has not undergone the studies necessary to show that it is indeed safe and effective for the particular use.

Most health practitioners would agree that off-label prescribing is appropriate and certainly falls under the auspices of the practice of medicine. Off-label prescribing is prescribing of a drug product for a use that is not a labeled use. Off-label promotion, on the other hand, is promoting a drug for a use that is not a labeled use with the goal of encouraging off-label prescribing. Many people argue that off-label uses are appropriate and beneficial to patients, and therefore, off-label prescribing should remain. In fact, the FDA has never forbidden off-label prescribing.[24] Often times certain uses present themselves after the drug has been on the market, or for a condition that the drug company did not consider when obtaining initial drug approval.

The significant expense and time associated with clinical trials to obtain a labeled indication, creates incentives for drug companies to enter the market with fewer indications rather than waiting for clinical evidence of effectiveness with multiple indications. One study estimates that research and development costs related to bringing

[23] MARK C LEVY, OFF-LABEL COMMUNICATIONS: A GUIDE TO SALES & MARKETING COMPLIANCE 1, FOOD AND DRUG LAW INSTITUTE (2d Edition) (2009).
[24] *Id*. at 2–3.

a new drug to the point of marketing approval was $802 million in 2000.[25] Furthermore, there is no guarantee that the drug will end up recovering the costs it incurred in gaining approval, and the sooner a company gets the drug on to market, the more time they have to recover their research and development costs.[26] As a result, most people would not expect pharmaceutical companies to study every single indication before gaining approval. The current system,[27] assuming the company is not using illegal promotional schemes, effectively allows off-label prescribing when it is in the best interest of the patient without unnecessary outside influences.

The decision to use the drug off-label should consist of sound clinical evidentiary reasoning, or on the experience of a physician who has seen improvements in patients using the drug. Conversely, when companies promote a drug for off-label uses by telling sales and marketing staff to promote the drug for an off-label use, the company is allowing non-medical professionals, whose jobs and compensation depend on how much product they sell, to promote a product that may or may not be effective or worse, safe, for the condition.

The FDA sends out warning letters when they discover that a company may be engaged in off-label promotional activities or other illegal schemes. These warning letters may or may not lead to a lawsuit.

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[25] DiMasi JA, Hansen RW, Grabowski HG. *The Price of Innovation: New Estimates of Drug Development Costs*. 22 J Health Econ, 151–185 (2003).

[26] A new molecular entity or drug entity has 20-years market exclusivity from the date of the NDA filing.

[27] Under the Food and Drug Administration Modernization Act of 1997, a drug company may directly distribute information "concerning the safety, effectiveness, or benefit of a use not described in the approved labeling of a drug or device" under specific circumstances. *See* 21 U.S.C. § 360aaa(a); *see also*, 21 C.F.R. § 99.1.

2.2.2 Medicare

Medicare and Medicaid are the two main health care programs that fund prescription drugs. An extraordinary number of complex regulatory provisions govern the federal health care programs.[28] The two government-funded entitlement programs must bear a substantial share of the cost of marketing, pricing, and other fraudulent schemes.

In 1965, Congress enacted Medicare[29] to pay for the costs of certain health care services. Medicare eligibility depends on age, disability, or a diagnosis of certain diseases.[30] The Secretary of Health and Human Services administers the Medicare program through the Centers for Medicaid & Medicare Services (CMS) (formerly the Health Care Financing Administration (HCFA).[31]

Under the Medicare program, eligible persons may enroll in Medicare Part A and B to obtain benefits for physician services, durable medical equipment (such as albuterol and other nebulizers) and certain pharmaceuticals.[32] Medicare Part A and B covers a

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[28] 42 C.F.R. § 1001.2(a)(2)(d). Federal health care program means any plan or program providing health care benefits, whether directly through insurance or otherwise, that is funded directly, in whole or part, by the United States Government (other than the Federal Employees Health Benefits Program), or any State health care program. *See* Mayo Chronicles Medicare Regs: It's 132,720 Pages of Red Tape, Modern Healthcare, Mar. 15, 1999, at 64 (stating that staff at one medical center counted 132,702 pages of Medicare laws and regulations).

[29] Title XVIII of the Social Security Act.

[30] *See* 42 U.S.C. § 1395-1395ccc (2006).

[31] Brief of the United States as Amicus Curiae Supporting Plaintiffs 3, *In re* Pharm. Indus. Average Wholesale Price Litig., MDL No. 1456, 491 F. Supp.2d 20 (D. Mass. June 21, 2007) (Civil Action No. 01-CV-12257-PBS).

[32] 42 U.S.C. § 1395k(a)(2)(B) (2008).

very limited number of pharmaceuticals.[33] The bulk of the expenditures used on Part B drugs are for injectable and intravenous drugs, such as intravenous cancer treatments furnished "incident to"[34] a physician's services.[35] Medicare Part A often reimburses hospitals for expenses related to inpatient prescription drugs.

Hospitals or clinics administer most of the drugs covered by Medicare Part A and B. Reimbursement in these settings occurs after the physician authorizes the administration of the drug. The physician or hospital or clinic administrator, based upon a complex coding system, submits a claim to the government for the drug used by the patient. The claim includes patient identifiers so that the reimbursement links to the specific patient who received the drug. The government then pays the claim for the drug to the hospital or clinic based upon the payment amount agreed upon using terms established by Congress.[36] Over the years, the number and types of prescription drugs covered under Part B has increased.[37]

As of January 1, 2006, every individual eligible for Medicare was also eligible for outpatient prescription drug coverage under Medicare Part D.[38] With the implementation

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[33] *See* 68 Fed. Reg. 50428, 50429 (Aug. 20, 2003).
[34] Section 1395(x)(s)(2) (2006) (provides that these "incident to" drugs (1) are not usually self administered, (2) are provided incident to a physician's professional services to patients in his office, (3) are of a kind commonly furnished in physicians' offices, and (4) are commonly rendered without charge or included in the physician's bill.) *See also* 42 U.S.C. 1395x(s)(2) (2006).
[35] 42 U.S.C. § 1395x(s)(2) (2006).
[36] This is an extremely brief explanation of reimbursement.
[37] The list now includes immunosuppressives, certain oral anti-cancer drugs, oral anti-emetic drugs, and influenza and hepatitis vaccines.
[38] The Medicare Prescription Drug, Improvement and Modernization Act of 2003 amended Title XVIII of the Social Security Act. *See* 42 U.S.C. § 1395w-101 (2006).

of Medicare Part D; the government expanded drug coverage to millions of seniors, and consequently, significantly increased the amount spent by the government on prescription drugs. Even before Medicare Part D went into effect, however, outpatient prescription drug spending throughout the U.S. grew faster than health care spending overall.[39]

In 1996, the total retail prescription sales in the U.S. were about $72 billion. By 2006, the sales number increased to nearly $250 billion.[40] The total number of outpatient prescriptions grew from 2.2 billion in 1996 to 3.4 billion in 2006.[41] With the implementation of Medicare Part D, spending by the government on prescription drugs has increased even more.[42] These increases emphasize the importance of preventing unnecessary spending by, among other things, curbing and preventing health care fraud.

There are specific criteria necessary for a drug company to get reimbursement for a drug prescribed to a patient. The way Medicare reimburses for drugs is important in

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Medicare Part D became available in January 2006. 42 U.S.C. § 1395w-101(a)(2) (2006).

[39] U.S. DHHS, Office of the Actuary, National Health Accounts, 2004 version, released January 2006.

[40] IMS Health data as reported by the National Association of Chain Drug Stores (May 7, 2007), available at http://www.nacds.org/wmspage.cfm?parm1=507. Total retail sales as defined by IMS Health includes outpatient prescription sales of independent pharmacies, traditional chain pharmacies, supermarket pharmacies, mass merchandiser pharmacies, and mail order pharmacies.

[41] *Id*.

[42] Centers for Medicare & Medicaid Services, *The 2008 Annual Report of the Boards of Trustees of the Federal Hospital Insurance and Federal Supplementary Medical Insurance Trust Funds* (2008). It is equally important to note that Medicare Part D is a relatively small part of the overall Medicare program. One estimate suggests, however, that Medicare is so large that Part D alone will account for 1% of the ENTIRE ECONOMY in less than 2 decades. *See also*, Centers for Medicare and Medicaid Services, National Health Expenditure Projections, 2006–2016: Forecast Summary (with selected tables), http://www.cms.hhs.gov/NationalHealthExpendData/downloads/proj2006.pdf (accessed Aug. 7, 2008)(stating that "U.S. health care spending is projected to total nearly $2.4 trillion in 2008, and nearly half will be government outlays").

understanding how off-label promotion leads to false claims. To be reimbursable by Medicare, a prescriber must prescribe a drug for an FDA-approved indication or for a "medically accepted indication."[43] A "medically accepted indication" is a use supported by one or more citations in one or two drug compendia or by "clinical evidence in peer reviewed medical literature appearing in publications which have been identified… by the Secretary [of Health and Human Services]."[44] The compendia are the United States Pharmacopoeia Drug Information (USP-DI), the American Society of Health-System Pharmacists (AHFS),[45] and the American Medical Association Drug Evaluations.

2.2.3 Medicaid

The second governmentally funded program, Medicaid, is an entitlement program for the poor or disabled. The various state and federal governments jointly fund Medicaid. Under federal law, the Medicaid program cannot cover the cost of prescription drugs unless the drug constitutes a "covered outpatient drug."[46] The definition of covered outpatient drugs excludes any drug not used for a "medically accepted indication."[47] A "medically accepted indication" is defined as a "use for a covered outpatient drug which is approved under the Federal Food, Drug & Cosmetic Act" (FDCA) or a use which is "supported by one or more citations included or approved for

[43] JOEL ANDROPHY, FEDERAL FALSE CLAIMS ACT AND QUI TAM LITIGATION § 506[1] (Law Journal Press-Litigation Series) (2008)[hereinafter ANDROPHY].
[44] ANDROPHY (quoting 42 U.S.C. § 1395x(t)(2)(B)(ii)(II) (2006)).
[45] *Id.*
[46] 42 U.S.C. § 1396b(i)(10) (2006).
[47] 42 U.S.C. § 1396r-8(k)(2)-(3).

inclusion in any of the compendia" listed in the statute.[48] Some commentators question the inclusion of Drugdex® as a compendia for determining the effectiveness of off-label uses because it lists an extraordinarily large number of acceptable off-label uses with more liberal criteria requirements as compared to the other two non-profit compendia.[49] A state may restrict or exclude coverage of a drug in four circumstances:

> (1) the prescribed use is not for a medically accepted indication; (2) the drug is on a list of drugs excluded by the state from Medicaid coverage; (3) the drug manufacturer agreed to the restrictions on the drug in its rebate agreement with Medicaid; or (4) the drug was excluded from the state's drug formulary.[50]

In general, Medicaid will reimburse for off-label uses as long as the prescriber states that it is medically necessary.

Off-label Promotion: Impact on Government Programs

Because the government reimburses companies for the majority of claims for off-label uses, using inappropriate promotional schemes causes Medicaid and Medicare to pay for an inflated number of prescriptions in violation of the False Claims Act (FCA). These schemes or tactics cost Medicaid/Medicare and the taxpayers that fund it, valuable resources, and consequently, these resources are wasted. In response, the government established certain laws to protect the taxpayer-funded resources of the federal and state health care programs. Two of these laws, the FDCA and the FCA provide the legal basis

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[48] *See* 42 U.S.C. § 1396r-8(k)(6); *see also* 42 U.S.C. § 1396r-8(g)(1)(B)(i) (identifying compendia as American Hospital Formulary Service Drug Information, United States Pharmacopeia-Drug Information and the DRUGDEX Information System).

[49] ANDROPHY at § 5.06[1](6) n. 17 (stating that the two non-profit compendia generally restrict listings to off-label uses that are supported by randomized, double-blind, and controlled studies). A district court in the Southern District of Florida found that drugs listed in DRUGDEX could not be

[50] ANDROPHY, at § 5.06[1](b); 31 U.S.C. § 1396r-8(d)(1).

by which pharmaceutical companies are liable for promoting a drug for an off-label use, and other fraudulent schemes. A discussion of the FDCA, FCA, and other pertinent legislation is included below.

2.2.4 The Food, Drug, and Cosmetic Act

The United States Federal Food, Drug, and Cosmetic Act (FDCA) of 1938 gave authority to the FDA to oversee the safety of food, drugs, and cosmetics. The FDCA prohibits distribution of drugs into interstate commerce unless the FDA approved the drug as safe and effective for each of its intended uses.[51]

The component of the FDCA particularly important here is the language that prohibits off-label marketing and misbranding.[52] Where a drug company promotes a drug for uses not indicated on the drug's label, the drug constitutes a misbranded drug, and the distribution of the drug in interstate commerce, is illegal.[53] A misbranded drug includes one where the label does not contain, *inter alia*, "[s]tatements of all conditions, purposes, or uses for which such drug is intended."[54] If the company directly advertises the drug for off-label use or employs a third party to market or promote a drug for off-label uses, the drug is misbranded. When a drug company directly advertises a drug for a

[51] 21 U.S.C. §§ 355(a), 355(d).
[52] 21 U.S.C. § 331(d),355.
[53] *See* 21 U.S.C. § 331(a) & (d).
[54] 21 C.F.R. § 201.5.

particular use, it constitutes an "intended" use and, therefore, the FDCA[55] requires a use description on the drug's label.[56]

When a drug company promotes an off-label use, and physicians in turn prescribe the drug for such uses or based upon inaccurate statements, the Medicaid or Medicare program pays more for prescription drugs than it would if it paid only for approved uses. The theory is that illegal promotional activities lead prescribers to prescribe drugs for uses that they would not otherwise write for, and thus, the company violation has caused the presentation of false or fraudulent claims to the Medicaid/Medicare program.[57] Allegations of off-label promotion rarely, if ever, occur if the drug involved is available as a multi-source generic product. In general, companies spend negligible amounts on marketing or promoting a prescription drug that has AB-rated generic competition.

2.2.5 The Food and Drug Administration Modernization Act

Prior to the Food and Drug Administration Modernization Act (FDAMA) of 1997[58], the FDCA expressly prohibited off-label promotion.[59] The FDAMA created a safe harbor provision that allows pharmaceutical companies to distribute off-label information about their drugs under the following requirements:

> (1) submission of a supplemental new drug application ("NDA") for such use;
> (2) dissemination of information that is not abridged, false, misleading, or posing a significant risk to the public health;

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[55] 21 U.S.C § 321.
[56] *See* 21 C.F.R. § 201.128 (stating that this objective intent may, for example, be shown by labeling claims, advertising matter, or oral or written statements by such persons or their representatives).
[57] The Role of the False Claims Act at 6.
[58] Food & Drug Admin. Modernization Act, 21 U.S.C. § 355 (2000 & West. Supp. 2000) (codified as amended at Pub. L. No. 105-115, 111 Stat. 2356 (1997)).
[59] See 21 U.S.C. §§ 355(a).

> (3) all clinical research found in the dissemination materials is the work of the manufacturer or with permission from the manufacturer of the work;
> (4) submission of a copy of the material to the Secretary of HHS at least sixty days prior to dissemination; and
> (5) inclusion in all disseminated materials prominent disclaimers clarifying that the information disclosed, "concerns a use of a drug that has not been approved or cleared by the FDA" for that particular use.[60]

Information about a new use that a company may disseminate includes:

> (1) an unabridged reprint or copy of an "article, peer-reviewed by experts qualified by scientific training or experience to evaluate the safety or effectiveness of the drug or device involved, which was published in a scientific or medical journal… which is about a clinical investigation with respect to the drug or device, and which would be considered to be scientifically sound by such experts";[61] and
> (2) an unabridged "reference publication"[62] "that includes information about a clinical investigation with respect to the drug or device that would be considered to be scientifically sound by experts qualified by scientific training or experience to evaluate the safety or effectiveness of the drug or device that is the subject of such a clinical investigation."[63]

The safe harbor provisions represented the first time that Congress expressly authorized the dissemination of journal articles about off-label uses to prescribers from drug manufacturers. The information does not apply to unsolicited requests for information from prescribers to the pharmaceutical company.[64] In addition, the following types of information are not considered scientifically sound for dissemination: letters to the editor, abstracts of a publication, articles regarding Phase I trials in healthy people, publications that "contain little or no substantive discussion of the relevant

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[60] 21 U.S.C. § 360(a) (2006)
[61] 21 U.S.C § 360aaa-1(a)(1)(A). *See also* 21 C.F.R. § 99.3(g); MICHAEL K. LOUCKS & CAROL C. LAM, PROSECUTING AND DEFENDING HEALTH CARE FRAUD CASES 2007 SUPPLEMENT (59), (BNA books) (2007), at 164 [hereinafter LOUCKS & LAM].
[62] *Id.*; 21 U.S.C. § 360aaa-1(b).
[63] *Id.* 21 U.S.C. § 360aaa-1(a)(1)(B). *See also* 21 C.F.R. § 99.101(a)(2)(ii)
[64] 21 C.F.R. §99.1(b)

clinical investigation," and publications regarding observations in four or fewer people "that do not reflect any systematic attempt to collect data, unless the manufacturer demonstrates to FDA that such reports could help guide a physician."[65] If the pharmaceutical company does not comply with the safe harbor provision, the company is subject to liability under the FDCA.

The safe harbor provisions do not apply to unsolicited requests for information from prescribers to the pharmaceutical company.[66] Thus, unsolicited requests could still constitute evidence of criminal or civil liability under the FDCA. Information about a new use that manufacturers could disseminate included unabridged reprint or copies from a peer-reviewed article and reference publications.[67] Again, the information could not be "false or misleading"[68] and "not pose a significant risk to the public health."[69] And, more importantly, the drug company was required to submit a supplemental application to the FDA on that use.[70]

According to the FDA Guidance to the Industry, "if these conditions were met, dissemination of such journal articles or reference publications would not be considered as evidence of the manufacturer's intent that the product be used for an unapproved new

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[65] 21 C.F.R. § 99.101(b)(1)(i-v); see also LOUCKS & LAM..
[66] 21 C.F.R. §99.1(b)(2006).
[67] LOUCKS & LAM at 163.
[68] 21 C.F.R. § 99.101(a)(4) (2008)(stating that the FDA may consider information "false and misleading" if, among other things, "the information includes only favorable publications when unfavorable publications exist.")
[69] 21 U.S.C. § 360aaa-1(a)(2) (2006); 21 C.F.R. §99.101(a)(3),(4) (2008).
[70] *Id.*

use."[71] Assuming that the promotional tactics of the drug company do not fall within the safe harbor provisions, the off-label promotion is not protected, and may be used by prosecutors as evidence of intent to promote or market a drug for off-label uses. The safe harbor, therefore, was important to drug companies because as long as they followed the safe harbor requirements, promoting off-label uses did not constitute evidence of FDCA or even False Claims Act violations.

Before Congress passed the FDAMA, the FDA expressed reservations about relaxing the restrictions on off-label promotion of drug and devices. The Deputy Commissioner for Policy testified on behalf of the FDA,[72] and described some of the limitations to the peer-review journal process:

> For example, peer reviewers almost never receive the study protocol. They cannot tell what the initial hypothesis was or whether the final analysis represents the planned analysis or an analysis crafted with the results in hand. Peer reviewers do not have access to the underlying data. The peer reviewers must rely on the data and facts as they are presented by the author. FDA, on the other hand, does have access to the data and can verify the critical statistical outcomes and the conclusions of a study. Moreover, peer reviewers do not necessarily have the time or the expertise in all aspects of the subject matter to adequately review the information. In fact, a survey reveals that a peer reviewer spends on average less than three hours reviewing a prospective article. The peer review process cannot guarantee the correctness or authenticity of the article, nor can it detect fraudulent or flawed research.[73]

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[71] Guidance for Industry, Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices U.S., January 2009.
[72] Senate Committee on Labor and Human Resources, Testimony of Deputy Commissioner For Policy, Food And Drug Administration William B. Schultz, Hearing on Unapproved Prescription Drugs and Medical Devices, l05th Cong. (Feb. 22, 1996).
[73] *Id.*

It is not clear how much emphasis Congress placed on the testimony of the FDA's designated voice prior to passing the FDAMA, but the safe harbor provisions did require supplemental applications on the off-label uses submitted to the FDA, and required submission of a copy of the journal article to Health and Human Services sixty days prior to dissemination of the article to prescribers.[74]

2.2.6 Post FDAMA: FDA Guidance on Off-label Promotional Materials

This section provides a history of off-label promotional regulation in the U.S. beginning with the Washington Legal Foundation's challenge to the first FDA Guidance to the industry on reprint practices. The section also describes the differences between older versions of the FDA Guidance document that were challenged by the Washington Legal Foundation, and the new 2009 FDA Guidance document that the Washington Legal Foundation has threatened to challenge on constitutional grounds.

Washington Legal Foundation

After the FDAMA became effective, questions arose concerning whether the injunction placed on the FDA Guidance document applied to the FDAMA safe harbor provisions. The Washington Legal Foundation continued its First Amendment challenge against the FDA for its Guidance document after enactment of the FDAMA.[75] In *Friedman (WLF II)*, the district court held that the district court's injunction in *WLF I* applied to the underlying policies of the FDA, not just the Guidance document.[76] *WLF II*

[74] 21 U.S.C. § 360aaa-1(a)(2) (2006).
[75] *Friedman (WLF II)*, 13 F.Supp. at 58.
[76] Washington Legal Foundation v. Leavitt, 477 F.Supp. 2d 202, 333 (D.D.C. 2007).

also held that the policy for dissemination of off-label materials constituted commercial speech, and thus, the FDA Guidance document violated a prescriber's First Amendment right to receive information about off-label uses from manufacturers.[77] The district court enjoined the FDA from enforcing policies restricting certain forms of manufacturer promotion of off-label uses.[78] The FDA asserted unsuccessfully that the FDAMA superseded the Guidance document, and therefore, the previous injunction should only apply to the Guidance document.[79] The district court rejected this assertion and held that the underlying policy and guidance of restricting dissemination of materials was unconstitutional.[80] In *Washington Legal Foundation v. Henney*, 56 F.Supp.2d 81 (D.D.C. 1999)(*WLF III*), the district court also found the safe harbor provisions of the FDAMA unconstitutional on First Amendment grounds.

The FDA appealed the holding,[81] and the "stage therefore appeared set for us to consider a difficult constitutional question of considerable practical importance. However, as a result of the government's clarification at oral argument, the dispute between the parties has disappeared before our eyes."[82] The FDA took the position that the off-label speech restrictions in the FDAMA and the corresponding rules established only a "safe harbor," that is, a procedure for manufacturers to distribute these materials without facing prosecution under the misbranding provisions of the FDCA.[83]

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[77] *Friedman (WLF II)*, 13 F.Supp. 2d at 58.
[78] *Id.*
[79] *Id.*
[80] *Id.*
[81] *Id.*
[82] *Leavitt*, 477 F.Supp. 2d at 335.
[83] *Henney (WLF III)*, 202 F.3d at 337.

Considering the change in position, WLF no longer took issue with the safe harbor provision of the FDAMA and dropped its constitutional challenge.[84] Subsequently, the DC Circuit Court dismissed the appeal and vacated the district court's injunction.[85]

Sunset of § 360aaa

In September of 2006, Congress allowed 21 U.S.C. § 360aaa to expire, removing the safe harbor provision from the FDAMA. Thus, since September of 2006, Congress has not provided guidance on dissemination of off-label materials for either the drug or medical device industry.

In April of 2007, the FDA held a meeting with drug industry advocates. According to a letter sent to the Commissioner of the FDA, Andrew C. von Eschenbach, from Representative Henry A. Waxman, Chair of the Committee on Oversight and Government Reform, U.S. Congress, the FDA meeting held on April 13, 2007 stated drug industry concern over the sunset of the safe harbor provisions of the FDAMA. The meeting summary is as follows:

> After introductions, Mr. Troy (Dan Troy is a former FDA chief counsel now representing drug companies) explained that Sidley Austin represents a number of companies that are concerned about dissemination of peer-reviewed journal articles. FDAMA allowed the practice of distributing this information, but the provision has now sunset. Sidley Austin spoke about their perceptions as well as the effect and consequences of the sunset provision. Mr. Kalb provided an overview of the problems companies face. He also expressed concerns about Federal prosecutors pursuing distributors of this information for criminal misconduct. There is confusion about the rules, possibly an FDA guidance could clarify the rules.[86]

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[84] *Id.*
[85] *Id.*
[86] Memorandum from Stephen R. Mason, Department of Health and Human Services, Food and Drug Administration to Henry Q. Waxman, Chairman Committee on Oversight

Five months after representatives from the drug industry spoke with the FDA Commissioner and other high-ranking officials of the FDA, the FDA distributed a draft document during fourth quarter 2007 entitled, "Guidance for Industry: Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices."[87] After a two-year comment period, the FDA released an official FDA Guidance to the Industry document.

2009 FDA Guidance for the Industry

The new FDA Guidance document allows a manufacturer to disseminate scientific articles on unapproved uses as long as they are following stated criteria.[88] The language of the Guidance resembles the language used in the safe harbor provisions of the FDAMA. The criteria for article dissemination includes, among other things, that the article be published in peer-reviewed journals, not including supplements or other publications paid for by the manufacturer; not be false or misleading; not be abridged or summarized by the manufacturer; be accompanied by approved labeling for the product; be accompanied by a

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and Government Reform, House of Representatives, dated December 21, 2007: attached Memorandum of Meeting April 13, 2007 Washington DC.

[87] FDA Guidance for Industry, Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices U.S., Draft Guidance- September or October 2007 (the draft noted that this guidance document was being distributed for comment purposes only.)

[88] Guidance for Industry, Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices U.S., January 2009.

bibliography of previously published studies of the unapproved use; if the article has been called into question by other articles, be accompanied by a representative article reaching different conclusions; be distributed separately from promotional materials; and be accompanied by a number of disclaimers and disclosures.[89]

The stated purpose of the Guidance document balances the value of having new indications and intended uses for products approved or cleared by the FDA and the "important public health and policy justification supporting dissemination of truthful and non-misleading medical journal articles and medical or scientific reference publications on unapproved uses of approved drugs."[90]

2009 Guidance document differs from the FDAMA safe harbor provision

The 2009 FDA Guidance to the industry has three noticeable omissions that were present in the FDAMA safe harbor provisions before they sunset. First, the new recommendations do not distinguish between solicited and unsolicited requests for information from prescribers, contrary to the FDAMA safe harbor provisions that supplanted the FDA's last Guidance document.[91] In other words, the new recommendations allow manufacturers to disseminate off-label articles without specific requests for such information from the prescriber. In practice,

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[89] *Id.; see also,* Memorandum from Henry Q. Waxman, Chairman Committee on Oversight and Government Reform, House of Representatives, to Andrew C. von Eschenbach, Commissioner, U.S. Food and Drug Administration to dated November 30, 2007.
[90] *Id.* at 3.
[91] *Id.* at 3, note 5.

this means that the manufacturer may target physicians and use other marketing tactics to get prescribers to use its drug for unapproved uses.

Second, the 2009 FDA Guidance does not require a copy submission to the Health and Human Services (FDA) sixty days prior to the dissemination of an article to prescribers. Third, the 2009 FDA Guidance does not require a supplemental application filing regarding the new use to the FDA. In other words, the FDA recommends that sales people disseminate articles to prescribers about new uses that the FDA has not reviewed, and that the FDA may never review for accuracy. The omission of these three recommendations suggests that the FDA is moving toward a minimal role in regulating off-label promotional activities.[92]

It is interesting how drastically the FDA's position on off-label promotion has changed. As stated earlier, in 1996, the then Deputy Commissioner for Policy at the FDA, William B. Schultz, testified before the Committee on Labor and Human Resources United States Senate regarding the proposed safe harbor provisions of the FDAMA. He expressed concerns about off-label promotion that the current FDA seems to dismiss. Schultz remarked that the FDA does not control the practice of medicine.

For instance, physicians have access to information about off-label uses through compendia, journal articles, continuing medical education programs,

[92] Randall S. Stafford, *Regulating Off-Label Drug Use – Rethinking the Role of the FDA*, 358(14) New Eng. J. Med. 1427 (2008).

symposia, and professional meetings.[93] They have access to countless databases that provide up to date information about off label uses such as the National Cancer Institute's Physician Data Query (PDQ) system, the National Library of Medicine (NLM), and the Medical Literature Analysis and Retrieval System (MEDLARS).[94] Most physicians carry PDA's that include programs, such as Micromedex®, that provide ratings on different off-label uses depending upon the literature, conflicting information, and the nature of the studies conducted. This information updates regularly. Most, if not all, hospitals provide free on-line resources and other drug information resources to prescribers, providing them with up to date access to information on unapproved new uses.

In 1996, the FDA appeared to take the stance that prescribers are more than capable of getting the information they need to serve their patients without outside influence on off-label uses by pharmaceutical sales representatives.

Policy makers and public health officials are not the only ones who expressed concern about the 2009 FDA Guidance. The Washington Legal Foundation, on behalf of the drug industry, expressed First Amendment concerns with the FDA Guidance draft document distributed in 2007. Historically, the drug industry has positioned its opposition to the FDA's involvement with regulating off-label promotion as a violation of the drug companies First Amendment right to freedom of speech.

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[93] *Id.*
[94] *Id.*

2011 DRAFT Guidance for Industry: Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices

In 2011, the FDA released another draft guidance on how manufacturers and distributors of prescription drugs and medical devices can respond to unsolicited requests for information about unapproved indications or conditions of use (off-label information) from the general public and prescribers.[95] According to the 2011 guidance document, if a pharmaceutical company responds to unsolicited requests for off-label information in the manner described, then it is highly unlikely the response would constitute evidence of off-label promotion.[96] Conversely, if a pharmaceutical company responds to unsolicited requests other than that recommended in the draft guidance, such activity could constitute evidence of off-label promotion.[97] The draft guidance also offers examples of what constitutes an "unsolicited" compared to a "solicited" request for off-label information noting that solicited requests "may be considered evidence of a firm's intent that a drug or medical device be used for a use other than that specifically approved or cleared by FDA."[98]

According to the Guidance document, information distributed in response to an unsolicited request should be accompanied by: a copy of the FDA-required labeling, if any; a prominent statement notifying the recipient that the FDA has not approved or

[95] Guidance for Industry Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices, DRAFT GUIDANCE, December 2011.
[96] *Id.* at 3.
[97] *Id.* at 3.
[98] *Id.* at 4-6. In a footnote, the document states that "activities that serve to solicit the requests for off-label information may themselves give rise to specific regulatory violations." *Id*. at 5, n. 7.

cleared the product as safe and effective for the said use; a prominent statement providing all important safety information including any boxed warning for the drug; a complete list of references for all of the information disseminated in the response.[99]

The main addition to the 2011 document was some guidance on responding to public unsolicited requests through the Internet or other electronic media. According to the Guidance document, pharmaceutical companies should only respond to requests that specifically name their product, in which case, the information provided in the public response should only include the company's contact information for the medical or scientific personnel or department so that the person can follow-up about the off-label use of the product through a non-public, one-on-one communication.[100]

2.2.7 Medicare Prescription Drug, Improvement, and Modernization Act

This Act created a new Medicare entitlement program called Medicare Part D that pays for outpatient prescription drugs for those eligible to receive Medicare benefits.[101] The prescription drug benefit went into effect on January 1, 2006.

2.2.8 Anti-kickback Statute

The Anti-kickback statute states that the offer or payment of anything of any value to any person if any one purpose is to influence the sale, purchase, or utilization of goods and services paid for by the federal healthcare system is illegal.[102] In other words, prohibited pharmaceutical companies from providing financial incentives to physicians

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[99] Guidance for Industry Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices, Draft Guidance, December 2011, at 9.
[100] *Id*. at 11.
[101] Pub. L. No. 108-173, 117 Stat. 2066 (Dec. 8, 2003).
[102] 42 U.S.C. § 1320a-7b(b)(1)-(2) (2006).

that may undermine the physician's independent medical judgment. A pharmaceutical company violates the Medicaid Anti-kickback provision[103] by causing the submission of false claims tainted by kickbacks.[104] When a violation of the Anti-kickback statute results in the submission of a claim for payment under Medicare or Medicaid, FCA liability exists.[105] There is a safe harbor put into place that allows some activities to fall outside the statute.

> The Anti-kickback statute:
> is extremely broad. The types of remuneration covered specifically include kickbacks, bribes, and rebates made directly or indirectly, overtly or covertly, or in cash in kind. In addition, prohibited conduct includes not only remuneration intended to induce referrals of patients, but remuneration also intended to induce the purchasing, leasing, ordering, or arranging for any good, facility, service, or item paid by Medicare or State health care programs.[106]

2.2.9 False Claims Act

The presentation of false claims falls within the jurisdiction of the False Claims Act (FCA).[107] Congress enacted the FCA in 1863, and amended it in 1986. The FCA is the primary civil tool used to combat health care fraud against the U.S.[108] There is plenty

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[103] 42 U.S.C. § 1320a-7b(b).
[104] ANDROPHY, at § 5.08[1][e].
[105] *Id.*
[106] Issuance of Final Rules Implementing the Anti-Kickback Statute, 56 Fed. Reg. 35952 (July 29, 1991) (to be codified at 43 C.F.R. pt. 1001).
[107] *See* U.S. *ex rel*. Franklin v. Parke-Davis, 147 F. Supp. 2d 39 (D. Mass. 2001) and U.S. *ex rel*. Hess v. Sanofi-Synthelabo, Inc., 2006 WL 1064127 (E.D. Mo. April 21, 2006).
[108] LOUCKS & LAMB, at 55. "One of the most powerful tools in that effort is the False Claims Act, which the Justice Department has used to recover approximately $2.3 billion since January 2009 in cases involving fraud against federal health care programs." *See also*, Press Release, Department of Justice Office of Public Affairs, Novartis Vaccines & Diagnostics to Pay More Than $72 Million to Resolve False Claims Act Allegations Concerning TOBI (May 4 2010).

of controversy over the legality and range of the FCA in off-label marketing cases.[109] Off-label marketing or misbranding allegations, however, successfully use the FCA as a tool in litigation matters.[110] Using the FCA as a tool for prosecuting allegations of pricing schemes is more straightforward because these allegations usually involve pricing that is readily available in the marketplace.

The FCA[111] creates civil liability for submitting a false claim, for making a false statement to get a false claim paid, and for conspiring to get a false claim paid.[112] These requirements generally require proof of the following elements: the submission of a claim to the U.S., the falsity of the claim, and knowledge of the falsity of the claim.[113]

In some health care fraud cases involving pricing schemes, the pharmaceutical company may use the government's knowledge of such activity as a defense.[114] For instance, in defense of submitting false pricing claims to the government, drug companies may argue that the government knew that the AWP was not an accurate benchmark of actual costs of the product, and that this knowledge did not induce the government to change their reimbursement policies. Because of this knowledge, the company may use the defense that the government's knowledge defeats the falsity requirement of the claim, a defense that has met varying levels of success.[115]

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[109] *See* Henry F. Fradella, 44 No.2 CRIM.L.BULL. 7.
[110] MICHAEL K. LOUCKS & CAROL C. LAM, PROSECUTING AND DEFENDING HEALTH CARE FRAUD CASES 2007 SUPPLEMENT (BNA books) (2007)[hereinafter LOUCKS & LAM SUPPLEMENT].
[111] 31 U.S.C. § 3729.
[112] LOUCKS & LAM SUPPLEMENT.
[113] *Id*.; U.S. *ex rel*. Lamers v. City of Green Bay, 168 F.3d 1013, 1018 (7th Cir. 1999).
[114] LOUCKS & LAM SUPPLEMENT at 60.
[115] *Id.*

The FCA involves claims submitted either directly or indirectly for payment by the U.S. government that are false and which the submitter knew or should have known to be false.[116] Liability for both a "false claim" and a "fraudulent claim" may require showing that what makes the claim either false or fraudulent is material to the asserted claim of entitlement to receive money or property from the government.[117] Nothing in the FCA explicitly states that the false claim must be material to the payment decision.[118]

Violations of the FCA allow the government to recover civil penalties of up to $11,000 for each violation, plus three times the amount of the damages sustained.

Penalties in more detail

The stakes are high for pharmaceutical companies. If convicted of criminal violations, an entity, or person is potentially subject to imprisonment, restitution, monetary fines, and mandatory exclusion. If convicted civilly, an entity, or person is potentially subject to treble damages, monetary fines, permissive exclusion, and surveillance with Corporate Integrity Agreements. In theory, the penalties, when used, should discourage fraudulent activities.

Exclusion Remedy

From the start, the exclusion remedy was intended to protect Medicare, Medicaid, and other Federal programs from "fraud and abuse, and to protect the beneficiaries of those programs from incompetent practitioners and from inappropriate or inadequate

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[116] 31 U.S.C. 3729.
[117] U.S. *ex rel.* Wilkins v. N. Am. Constr. Corp. 173 F.Supp.2d 601, 626 (S.D. Tex. 2001).
[118] LOUCKS & LAM SUPPLEMENT at 60.

care."[119] In 1977, Congress first mandated the exclusion of physicians and other practitioners convicted of program-related crimes from participation in Medicare and Medicaid.[120] Congress addressed exclusion penalties again in 1981 with the passage of the Civil Monetary Penalties Law (CMPL).[121] The CMPL authorizes the U.S. Department of Health and Human Services and the Office of Inspector General[122] to exclude individuals and entities who submit false or fraudulent, or otherwise improper claims[123] for Medicare or Medicaid payment.[124]

The government expanded exclusion principles again in 1987 with the implementation of the Medicare and Medicaid Patient and Program Protection Act (MMPPPA). Concern that patients needed greater protection from physicians who would lose their license to practice medicine in one state and then simply transfer to another state where they would continue to practice prompted the expansion.[125] The 1980's amendments suggest that the intent of the legislators was to curb fraud and abuse by more

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[119] S. Rep. No. 109, 100th Cong., 1st Sess. 1-2 (1987), reprinted in 1987 U.S.C.C.A.N. 682, 684; *see also* Pamela H. Bucy, Civil Prosecution of Health Care Fraud, 30 WAKE FOREST L. REV. 693, 721-22 (1995).

[120] *See* Special Advisory Bulletin, Medicare-Medicaid Anti-Fraud and Abuse Amendments, Pub.L. 95-142. *See also*, U.S. Department of Health and Human Services: Office of Inspector General, The Effect of Exclusion From Participation in Federal Health Care Programs (Sept. 1999).

[121] *Id*. and Pub.L. 97-35. *See also*, 42 U.S.C. 1320a-7a (CMPA).

[122] In 1983, the Secretary of Health and Human Services delegated the responsibility to detect, prosecute, and punish fraudulent acts under Medicare and Medicaid to the Office of Inspector General. *See also,* Greene v. Sullivan, 731 F. Supp. 835, 837 (E.D.Tenn. 1990).

[123] Improper claims "includes claims submitted by an excluded individual or entity for items or services furnished during a period of program exclusion."

[124] *Id*.

[125] Pamela H. Bucy, *Civil Prosecution of Health Care Fraud*, 30 Wake Forest L. Rev. 693, 721-22 (1995).

direct providers such as physicians, rather than the large corporate conglomerates that exist today.

The MMPPPA of 1987[126] established two different types of exclusion: mandatory and permissive. Mandatory exclusion[127] requires a 5-year minimum exclusion for any

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[126] 42 U.S.C. § 1320a-7 (1988 & Supp. V 1993); 1987 U.S.C.C.A.N. 684.

[127] 42 U.S.C. 1320a-7(a)(2006).

The Secretary *shall* exclude the following individuals and entities from participation in any Federal health care program (as defined in section 1320a-7b(f) of this title):

> (1) Conviction of program-related crimes:
> Any individual or entity that has been convicted of a criminal offense related to the delivery of an item or service under subchapter XVIII of this chapter or under any State health care program.
>
> (2) Conviction relating to patient abuse
> Any individual or entity that has been convicted, under Federal or State law, of a criminal offense relating to neglect or abuse of patients in connection with the delivery of a health care item or service.
>
> (3) Felony conviction relating to health care fraud:
> Any individual or entity that has been convicted for an offense which occurred after August 21, 1996, under Federal or State law, in connection with the delivery of a health care item or service or with respect to any act or omission in a health care program (other than those specifically described in paragraph (1)) operated by or financed in whole or in part by any Federal, State, or local government agency, of a criminal offense consisting of a felony relating to fraud, theft, embezzlement, breach of fiduciary responsibility, or other financial misconduct.
>
> (4) Felony conviction relating to controlled substance:
> Any individual or entity that has been convicted for an offense which occurred after August 21, 1996, under Federal or State law, of a criminal offense consisting of a felony relating to the unlawful manufacture, distribution, prescription, or dispensing of a controlled substance.

individual or entity convicted of certain offenses, such as a felony conviction in connection with the delivery of health care items or criminal offenses related to the delivery of an item under Medicare or Medicaid.[128] The lone exception to mandatory exclusion is situations where the individual or entity is the only source of "essential specialized services" or the sole physician in a community.[129] In contrast to mandatory exclusion, the Secretary has discretion on whether to use permissive exclusion for certain offenses, such as misdemeanor fraud conviction.[130]

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[128] *Id.*

[129] Micheal K. Loucks & Carol C. Lam, Prosecuting and Defending Health Care Fraud Cases, 438 Bureau of National Affairs, Inc. (June 2006)[hereinafter Loucks & Lam 2006](citing 42 U.S.C. § 1320(a)-7 (2008))(citing to 42 U.S.C. § 1320a-7(c)(3)(B)(2008).

[130] 42 U.S.C. § 1320a-7 (2008). The following text is incomplete:

> (b) Permissive exclusion
> The Secretary *may* exclude the following individuals and entities from participation in any Federal health care program (as defined in section 1320a-7b(f) of this title):
> (1) Conviction relating to fraud
> Any individual or entity that has been convicted for an offense which occurred after August 21, 1996, under Federal or State law--
> (A) of a criminal offense consisting of a misdemeanor relating to fraud, theft, embezzlement, breach of fiduciary responsibility, or other financial misconduct--
> (i) in connection with the delivery of a health care item or service, or
> (ii) with respect to any act or omission in a health care program (other than those specifically described in subsection (a)(1) of this section) operated by or financed in whole or in part by any Federal, State, or local government agency; or
> (B) of a criminal offense relating to fraud, theft, embezzlement, breach of fiduciary responsibility, or other financial misconduct with respect to any act or omission in

The final changes to exclusion provisions went into effect with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and the Balanced Budget Act (BBA) of 1997.[131] The 1996 and 1997 Acts extended the application and scope of the exclusion authorities beyond programs funded by the Department (Medicaid and Medicare) to all "federal health care programs."[132] HIPAA also expanded the category of defendants subject to mandatory exclusion.[133]

In accordance with the expanded sanctions authorized by these two statutes, an exclusion from the federal health care programs prevents an entity or individual from "being under contract with any practitioner, provider or supplier to provide items and services reimbursed by a federal health care program."[134] Health care providers consider exclusion the "death penalty"[135] because prohibiting reimbursement from the government could potentially put the individual or entity out of business.[136]

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a program (other than a health care program) operated by or financed in whole or in part by any Federal, State, or local government agency. *See also,* 42 C.F.R. § 1001.201

[131] Pub. L. No. 100-93.

[132] *See* Medicare-Medicaid Anti-Fraud and Abuse Amendments, Pub.L. 95-142. *See also*, Special Advisory Bulletin, U.S. Department of Health and Human Services: Office of Inspector General (Sept. 1999). The Effect of Exclusion From Participation in Federal Health Care Programs.

[133] Loucks & Lam 2006 at 438 citing 42 U.S.C. § 1320(a)-7)(2008).

[134] *Id*. *See also,* Rebecca Walker 1536 PLI/Corp 667 Practicing Law Institute ASSESSING YOUR COMPLIANCE AND ETHICS PROGRAM (POWERPOINT)March-June, 2006 at711 (stating that the effect of exclusion can be profound)

[135] Loucks & Lam 2006 at 52(stating that administrative exclusion from program participation is the "death penalty" for corporate providers).

[136] Corporate Crime Reporter, The Top 100 False Claims Act Settlements, Taxpayers Against Fraud Education Fund at 3 (2003). Subjects of federal health care fraud investigations have well founded concerns that resulting monetary and exclusion sanctions could threaten the providers' very existence.

Government reports from the late 1990's suggest that the expansions provided under HIPAA triggered increases in the number of individuals and entities excluded. In the fiscal year 1999, three years after the enactment of HIPAA, HHS/OIG excluded 2,976 individuals and entities from reimbursement through the federal health care programs.[137] In the fiscal year 2006, the HHS/OIG excluded a total of 3,422 individuals and entities from the federal health care programs.[138] HHS/OIG has only excluded one pharmaceutical entity from 1996 through 2006 and that was a subsidiary of a company that continued to get reimbursed through government programs (Schering Sales Corporation).[139]

HIPAA also established a national Health Care Fraud and Abuse Control Program (HCFAC or the Program) under the joint direction of the Attorney General, and the Secretary of the Department of Health and Human Services (HHS).[140] Both the Attorney General and Secretary act through the Department's Inspector General (HHS/OIG).[141]

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[137] Loucks & Lam 2006 at 441(citing U.S. Dep't of Health & Human Servs. & Dep't of Justice, *Annual Report of the Department of Health and Human Services and the Department of Justice, Health Care Fraud and Abuse Control Programs FY 1999* (2000)).

[138] U.S. Dep't of Health & Human Servs. & Dep't of Justice, *Annual Report of the Department of Health and Human Services and the Department of Justice, Health Care Fraud and Abuse Control Programs FY 2006* (2008), available at http://www.oig.hhs.gov/publications/docs/hcfac/hcfacreport2006.pdf

[139] U.S. Department of Health & Human Services, Office of Inspector General, *Entities by Classification*: *HHS-OIG Fraud Prevention & Detection – Classification Details*, http://exclusions.oig.hhs.gov/ClassificationDetails.aspx?id=46 (last visited Oct. 29, 2008)

[140] U.S. Dep't of Health & Human Servs. & Dep't of Justice, Health Care Fraud And Abuse Control Program Annual Report For FY 1998 (1998), http://www.usdoj.gov/dag/pubdoc/98hipaa_ar.htm#a (last visited July 15, 2008)(stating that the Health Care Fraud and Abuse Control Program is a far-reaching program to combat fraud and abuse in health care, including both public and private health plans).

[141] *Id*.

The intent of the Program was to coordinate federal, state and local law enforcement activities with respect to health care fraud and abuse.[142] According to the HCFAC Program Annual Report, the 1996 legislation made available "much needed and powerful criminal and civil enforcement tools and financial resources that permitted the government to expand and intensify the fight against health care fraud."[143]

2.2.10 Best Price: False Claims Act; Medicaid Rebate Program

In 1990, Congress enacted the Medicaid Rebate Program in an effort to control the cost of drugs paid for under Medicaid. As a result of the Program's enactment, each drug manufacturer voluntarily entered into an agreement with the Secretary of HHS to pay rebates to the States based on the utilization of its drug products in exchange for Medicaid coverage of the drug manufacturer's products.[144] Under the Medicaid Program and resulting rebate agreement with HCFA, participating drug manufacturers were required: (1) to report to HCFA on a quarterly basis the "best price" for single source and innovator multiple source drugs, defined as "the lowest price available from the manufacturer during the rebate period to any wholesaler, retailer, provider, health maintenance organization, non-profit entity or governmental entity within the United States," with certain specified statutory exclusions;[145] (2) to determine best price by including, among other things, "free goods that are contingent on any purchase requirement;"[146] (3) to pay each State plan a quarterly rebate on single source and

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[142] *Id*.
[143] *Id*.
[144] 42 U.S.C. § 1396r-8(a)(1).
[145] 42 U.S.C. § 1396r-8(c)(1)(C)(i).
[146] 42 U.S.C. § 1396r-8(c)(1)(C)(ii)(I).

innovator multiple source drugs equal to the product of (a) the units of each dosage form and strength paid for under the State plan during the rebate period as reported by the state, and (b) the greater of (i) the difference between the average manufacturer price and the best price, or (ii) a minimum rebate percentage of the average manufacturer price.[147] The Program requirements have been amended and revised over time by various Acts of Congress.

2.3 The Government's Use of Non-monetary Tools to Combat Healthcare Fraud

2.3.1 Corporate Integrity Agreements (CIAs)

Since the mid-1990s[148], it has become standard practice for the OIG and DOJ to require health care providers and entities to enter into corporate integrity agreements (CIAs) when settling civil liabilities in exchange for the OIG's agreement not to seek the providers' exclusion from the federal health care programs.[149] Corporate integrity agreements generally last 5 years and combine elements common to all corporate

[147] 42 U.S.C. § 1396r-8(c)(1)(A).
[148] *See* Joan H. Krause, *A Conceptual Model of Health Care Fraud Enforcement,* 12 J.L. & POL'Y 55, 95 (2003)(stating that "one of the most significant recent developments in health care fraud and abuse has been the increasing emphasis on corporate compliance.")
[149] *See* Office of Inspector General, Corporate Integrity Agreements: General Information, http://oig.hhs.gov/fraud/cias.asp (last visited Oct. 22, 2008). As the OIG explains, "A provider or entity consents to these obligations as part of the civil settlement and in exchange for the OIG's agreement not to seek an exclusion of that health care provider or entity from participation in Medicare, Medicaid and other Federal health care programs.." *Id*. *See also,* Thomas E. Bartrum & L. Edward Bryant, Jr., *The Brave New World of Health Care Compliance Programs*, 6 Annals Health L. 51, 55 (1997) (explaining CIA requirements).

integrity agreements with facts specifically related to the conduct at issue.[150] Voluntary compliance programs began to formalize shortly after the introduction of the Federal Sentencing Guidelines for Organizations in 1991.[151] The OIG publishes a series of "Compliance Program Guidance," including one that directly speaks to practices within the pharmaceutical industry.[152] These voluntary programs are important because they provide a benefit to entities during settlement negotiations.[153] The entities benefit because a compliance program already in existence demonstrates that they view

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[150] *See* Office of Inspector Gen., Corporate Integrity Agreements: General Information, http://oig.hhs.gov/fraud/cias.asp (last visited Oct. 22, 2008).

> These compliance measures seek to ensure the integrity of Federal health care program claims submitted by the provider. The more comprehensive integrity agreements include requirements to:
>
> Hire a compliance officer/appoint a compliance committee; Develop written standards and policies; Implement a comprehensive employee training program; Retain an independent review organization to review claims submitted to Federal health care programs; Establish a confidential disclosure program; Restrict employment of ineligible persons; Report overpayments, reportable events, and ongoing investigations/legal proceedings; and Provide an implementation report and annual reports to the OIG on the status of the entity's compliance activities. *Id*.

[151] *See* Joan H. Krause, *A Conceptual Model of Health Care Fraud Enforcement*, 12 J.L. & POL'Y 55, 95 (2003)(citing U.S. Sentencing Guidelines Manual ch. 8 (sentencing of organizations) (2001)).

[152] Notices, Department of Health and Human Services, Office of Inspector General, *OIG Compliance Program Guidance for Pharmaceutical Manufacturers* 68 FR 23731 (May 5, 2003); Krause at 96–97.

[153] Krause at 96.

compliance as an important issue and have the tools in place to facilitate a Corporate Integrity Agreement with the government.

Not surprisingly, pharmaceutical entities probably prefer a Corporate Integrity Agreement versus mandatory or permissive exclusion from the federal health care programs because the company may continue to contract with Medicaid/Medicare under the guidance of the CIA. The Agreements' usefulness in deterring future activities, however, is not clear. It is common for the Department of Justice to utilize CIAs as part of the settlement. In contrast, the government's utilization of the exclusion remedy against pharmaceutical companies is, for all practical purposes, nonexistent.

As illustrated in the case examples that follow even where a pharmaceutical entity received a felony health care fraud conviction, mandating the use of exclusion against the company, the excluded entity was a subsidiary company, which allowed another branch of the pharmaceutical company to continue to contract with federal health care programs. In practical terms, the exclusion remedy used in such a way does not act as a deterrent.

2.3.2 Ineffective: attached to subsidiary/shell companies

In 2005, Swiss corporation, Serono, S.A., and its U.S. subsidiaries and related entities, agreed to pay $704 million to resolve criminal and civil allegations in connection with illegal schemes to promote, market and sell its drug, Serostim®.[154] Resulting from

[154] Press Release, Department of Justice, Serono To Pay $704 Million For The Illegal Marketing Of AIDs Drug (Oct. 17, 2005). Serostim® treats AIDS wasting, a condition involving profound involuntary weight loss in patients with AIDS. Under the settlement, Serono Laboratories agreed to pay a $136.9 million criminal fine and its affiliate companies a total of $567 million to settle civil liabilities. Serono Labs agreed to plead guilty to charges that the company conspired with medical device manufacturer RJL Sciences to market computer software packages not yet approved by the FDA, for use in

its criminal conviction, Serono Labs, another subsidiary, received exclusion from all federal health care programs for five years.[155] Although the government barred Serono Labs from contracting with the federal health care programs, Serono Inc.'s branded products, including Serostim®, remained eligible for reimbursement under federal healthcare programs.[156]

In 2007, Purdue Fredrick Company, Inc. pled guilty to felony charges of misbranding the drug Oxycontin® (extended-release oxycodone) and settled other civil claims.[157] The felony conviction brings with it mandatory exclusion from federal health care programs. As part of the guilty pleas, the government barred Purdue Frederick Company from contracting with any of the federal health care programs for at least 5 years. Analogous to other settlement agreements with pharmaceutical companies that include violations with sentences requiring mandatory or permissive exclusion, however, a subsidiary company received the exclusion. The government attached the exclusion to a subsidiary company: Purdue Frederick Company. The main company, Purdue, was still able to contract with federal health care programs.

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calculating body cell mass and diagnosing AIDS wasting. Serono Labs conspired with RJL to increase the market for the devices/software in order to increase the market for Serostim®. Additionally, Serono Labs pled guilty to offering physicians an all expense-paid trip to a medical conference in France in return for the doctors writing up to 30 new prescriptions of Serostim®. At the time, Serostim® cost $21,000 per course of treatment, which resulted in a total value of $630,000 per doctor.

[155] *Id.*

[156] The Pink Sheet, *Serostim $704 Mil. Settlement Is Largest For Off-Label Marketing Case*, 67(43) FDC Reports 10 (Oct. 24, 2005).

[157] Press Release, U.S. Attorney's Office Western District Of Virginia, The Purdue Frederick Company, Inc. and Top Executives Plead Guilty to Misbranding Oxycontin; will Pay over $600 Million, (May 10, 2007) at page 1, available at http://www.usdoj.gov/usao/vaw/press_releases/purdue_frederick_10may2007.html.

Attaching the exclusion remedy to a subsidiary appears to be common practice by the government. Thus, even when the government utilizes the sort of guilty pleas that mandate exclusion, or when the government decides to utilize permissive exclusion, the remedy is largely a "symbolic gesture."[158] The Oxycontin® illustration demonstrates the ineffectiveness of exclusion in the context of pharmaceutical industry fraud.

2.3.3 Ineffective: as a deterrent

The following example demonstrates both the ineffectiveness of the exclusion remedy from the standpoint of actually excluding, and also, the ineffectiveness of this tactic in preventing or deterring future fraud against the federal health care programs. In 2004, the U.S. government entered into a settlement agreement with Schering-Plough,[159] arising from allegations of fraudulent marketing and pricing schemes involving the blockbuster drug, Claritin® (loratadine).[160] Schering Sales Corporation, the sales and marketing subsidiary of drug manufacturer Schering-Plough Corporation, pled guilty to criminal charges and paid a fine of $52.5 million for violating the Anti-Kickback Statute by paying a kickback to a customer in exchange for the preferred treatment of Claritin® on its formulary.[161] Schering-Plough Corporation paid more than $290 million to resolve

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[158] Adam Eckstein, The Pink Sheet, *Schering Corp. Accepts Federal Contract Ban Under Settlement*; 008 The FDC Reports, (July 30, 2004)(noting that the ban against Schering Sales Corp. was largely a symbolic gesture because Schering-Plough will continue to contract with the government.)

[159] Press Release, Department of Justice, Schering-Plough To Pay $345 Million To Resolve Criminal And Civil Liabilities For Illegal Marketing Of Claritin, (July 30, 2004).

[160] Loratadine is indicated for the treatment of allergy symptoms (seasonal allergic rhinitis) and chronic Idiopathic urticaria). Micromedex® Healthcare Series, DRUGDEX® Evaluations, *Loratadine*, accessed Oct. 25, 2008.

[161] Presss Release, Department of Justice, Schering-Plough To Pay $345 Million To Resolve Criminal And Civil Liabilities For Illegal Marketing Of Claritin (July 30, 2004).

civil liabilities stemming from its fraudulent pricing of Claritin®.[162] Schering Sales Corp., a subsidiary company of Schering-Plough, received a 5-year exclusion from entering into any contract with federal health programs.[163] "The ban appears to be the first during the recent round of government investigations into pharmaceutical marketing and pricing practices."[164] The parent company, Schering-Plough, Inc. continued to participate in government programs, and continued to sell Claritin® through the government programs.

Finally, just two years after Schering Sales Corporation took the fall for Schering-Plough, the subsidiary again pled guilty to allegations involving different drug products and tactics in 2006.[165] To resolve the criminal charges, Schering Sales Corporation pled

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[162] *Id*. The false claims act liabilities stemmed from Schering's failure to report it's true best price to the Medicaid programs in violation of the Medicaid Rebate Program.
[163] Adam Eckstein, The Pink Sheet, *Schering Corp. Accepts Federal Contract Ban Under Settlement*, 008 The FDC Reports 1 (Jul 30, 2004).
[164] *Id*.
[165] Medicare Drug Focus Weekly Business Intelligence, *Schering Subsidiary Takes Fall For Criminal Charges Under DoJ Settlement*, 2:36 FDC Reports (Sept. 4, 2006). See *also*, Press Release, Michael J. Sullivan, Department of Justice, Schering To Pay $435 Million For The Improper Marketing Of Drugs And Medicaid Fraud, (Aug. 29, 2006).

> The civil settlement resolves allegations that **SCHERING-PLOUGH CORPORATION** and **SCHERING SALES** knowingly caused the submission of false and/or fraudulent claims for Schering's drugs that were not eligible for reimbursement. These included the government's claims that (1) Schering misreported its best price to HCFA on Claritin ReidTabs to evade Medicaid rebate liability, (2) Schering misreported its best price on private-labeled K-Dur to HCFA to evade Medicaid rebate liability, (3) Schering overcharged the PHS entities because of its misreporting of best price to HCFA,

guilty to one count of criminal conspiracy to making false statements to both the FDA, regarding improper drug promotional activity, and to the Health Care Financing Administration (now CMS), regarding best price reporting for certain drugs.[166] The criminal conviction, like two years previously, mandated that Schering receive exclusion from federal health care programs. As the government had done two years earlier,[167] the government barred Schering Sales Corporation from participation in all federal health care programs, but this time, permanently.[168] Among other aspects of the settlement, Schering-Plough agreed to settle its civil FCA and FDCA liabilities for a total of $255,025,000.[169]

> (4) Schering induced physicians to start patients on Intron A for Hepatitis C by paying them remuneration through three marketing programs,
> (5) Schering induced physicians to use Temodar for certain patients with brain tumors and brain metastases and to use Intron A for certain patients with superficial bladder cancer through improper preceptorships, sham advisory boards, lavish entertainment, and improper placement of clinical trials; and
> (6) Schering knowingly promoted off label uses of Temodar for certain brain tumors and brain metastases and Intron A for superficial bladder cancer despite not having FDA approval.

[166] Press Release, Michael J.Sullivan, Department of Justice, Schering To Pay $435 Million For The Improper Marketing Of Drugs And Medicaid Fraud (Aug. 29, 2006).
[167] Under the previous agreement from two years prior, the Department of Justice had already excluded Schering Sales Corporation from contracting with the federal health care programs. Thus, Schering Sales Corporation could not contract with the federal health care programs at the time of the second settlement agreement so excluding the entity again did not make any sense.
[168] Press Release, Michael J.Sullivan, Department of Justice, Schering To Pay $435 Million For The Improper Marketing Of Drugs And Medicaid Fraud (Aug. 29, 2006).
[169] *Id.*

> The sales unit, which marketed and sold Schering-Plough products and employed its sales force, made the criminal plea despite being essentially eliminated in 2004 following a separate agreement with the Philadelphia U.S. Attorney's Office. Since the Philadelphia settlement, Schering Sales Corp. has been a legal entity with limited assets and no personnel because Schering-Plough shifted the employees of Schering Sales Corp. to another Schering-Plough division.[170]

Not surprisingly, Schering-Plough continued to participate in government programs under a revised CIA.[171]

In most cases, the government does not utilize the exclusion remedy against pharmaceutical companies, even though settlements from the past several years suggest that they encompass the largest monetary health care fraud recoveries. When "utilized" against pharmaceutical companies the exclusion remedy is ineffective for obvious reasons— the government bans subsidiary companies, and allows the main company to escape with monetary fines and a CIA.

The failure of the government to utilize exclusion and the ineffectiveness inherent in attaching exclusion to subsidiary entities supports the underlying premise of this study.

2.4 Off–label Promotion Literature

Since the heavily publicized Neurontin settlement in 2004, researchers have published several studies on off-label promotion and off-label prescribing in general. The focus has varied from studies that focus on examining off-label prescribing trends to studies that focus on examining specific fraud litigations for trends and associations. Many studies have demonstrated wide off-label use, especially concerning certain

[170] *Id.*
[171] *Id.*

therapeutic classes.[172] For instance, one study examined off-label prescribing of anticonvulsants, antidepressants, and antipsychotic agents finding a high frequency of off-label prescribing.[173]

In another study examining off-label prescribing, researchers found that off-label use was most common among cardiac medications (46%) and anticonvulsants (46%).[174] Out of the individual medications, gabapentin (83%) and amitriptylline hydrochloride (81%) were most frequently used off-label. Perhaps the most alarming conclusion was that for all drugs, including gabapentin, "[n]o more than 30% of the off-label practices observed were supported by strong scientific evidence."[175]

In yet another study examining the frequency of off-label prescribing for commonly prescribed drugs, researchers concluded that the strength of scientific

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[172] *See* Hampton T. *Experts weigh in on promotion, prescription of off -label drugs*. 297 JAMA 683-84 (2007); Morita T, Hori A, Narimatatsu H, et al. *Current status of development of anticancer agents in Japan*, 87 Int J Hematol 484-89 *(*2008); Dai C, et al., *National trends in cyclooxygenase-2 inhibitor use since market release: non-selective diffusion of a selectively cost-effective innovation*, 165(2) Arch Intern Med. 171-177 (2005).

[173] Chen H., et al. *Off-label Use of Antidepressant, Anticonvulsant, and Antipsychotic Medications Among Georgia Medicaid Enrollees in 2001*. 67(6) J Clin Psychiatry, 972 (June 2006).

[174] Radley DC, et. al. *Off-label prescribing among office-based physicians.* 166(9) Archives of Internal Medicine. 1021-1026 (2006). The researchers used 2001 IMS Health National Disease and Therapeutic Index (NDTI) as their source.

[175] *Id.* Mack, A., *Examination of the Evidence for Off-Label Use of Gabapentin* 9(6) JMCP (Nov/Dec 2003) at 559 (stating that in the majority of circumstances where it has reported potential for "off-label" use, gabapentin is not the optimal treatment). In another study, researchers found that only 19% to 57% of anticonvulsant off-label uses had evidentiary support from randomized, controlled trials. Chen H., et al. *An epidemiological investigation of off-label anticonvulsant drug use in the Georgia Medicaid population*, 14 J Pharmacoepidemiol Drug Saf 629-638 (2005).

evidence for the off-label prescribing was poor at best.[176] 73% of the estimated 21% of drug uses that were off-label failed to provide good scientific support for the off-label use.[177] Researchers attempted to determine whether such drug characteristics as manufacturer and annual sales levels predicted the likelihood of off-label prescribing, but found no association between these characteristics and the likelihood of off-label prescribing.[178]

These studies confirm the prevalence of off-label prescribing, which is a legal endeavor. However, many of the studies also show growth in off-label prescribing for uses where there is no scientific support.

The other set of publications on off-label prescribing concern some of the fraud lawsuits that are also the subject of this dissertation.[179] These studies provide background information on some of the settlements and specific aspects of some lawsuits such as interviews with the whistleblowers who initiated some of the lawsuits against

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[176] Radley D, et al.. *Off-label prescribing among office-based physicians*. 166 Arch Intern Med. 1021–6 (2006).
[177] *Id*.
[178] *Id*.
[179] Kesselheim AS and Studdert DM. *Whistleblower-initiated enforcement actions against health care fraud and abuse in the United States, 1996-2005, 149* Annals of Inter Med, 342-349 (2008); Kesselheim AS, et al., *Whistleblower-initiated enforcement actions against health care fraud and abuse in the United States*, 149 Ann Intern Med 342-9 (2008); Mello MM et al., *Shifting terrain in the regulation of off-label promotion of pharmaceuticals*, 360 N Engl J Med 1557-66 (2009); Qureshi ZP, et al., *Pharmaceutical Fraud and Abuse in the United States, 1996-2010*, 171(16) Arch Intern Med, 1503-505 (Sept 12, 2011); Qureshi ZP, et al., *Enforcement Actions Involving Medicaid Fraud and Abuse, 1996-2009*, 171(16) Arch Intern Med, 785-87 (Apr 25, 2011).

their former employers. Organizations such as Taxpayers Against Fraud Education Fund also publish papers and track fraud and abuse lawsuit information.[180]

Another study intended to determine whether the filing of a False Claims Act lawsuit or other events associated with the lawsuit correlated to a decline in utilization of the respective drug, in this case, gabapentin.[181] The researchers postulated that they would detect a deterrent effect evidenced by a decline in off-label utilization of gabapentin from the date the lawsuit was filed through to when the lawsuit was unsealed (sealed investigation period where the drug company knows it has been sued, but the information is not available publicly) and a further decline after the lawsuit was unsealed (made available publicly). The results of the study provided weak evidence that the settlement stage of the gabapentin prosecution produced a deterrent effect, but no evidence that any other stage did.[182] This study offers support for the reasoning behind using a timeframe from when the drug was first reimbursed through Medicaid to the last month before the settlement date.

As demonstrated above, although law and regulations intended to make the government whole while deterring future misconduct are in place, no evidence exists to demonstrate that such laws and regulations deter future health care fraud allegations within the pharmaceutical industry. This study relies on the hypothesis that settlements amounts are not associated with the dollars spent by Medicaid programs for the drug, among other factors.

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[180] See www.taf.org.
[181] Kesselheim, AS, *et al*., *False Claims Act Prosecution Did Not Deter Off-label Drug Use in the Case of Neurontin*, 30(12) Health Affairs, 2318-27 (December 2011).
[182] *Id*. at 2324.

CHAPTER 3
RESEARCH STUDY DESIGN AND METHODS

3.1 Theoretical Models:

3.1.1 Profit Maximization and/or Guardians of Patient Health

The conceptual framework for this study is the profit maximization theory and the 'justice model'. The profit maximization theory explains why companies engage in allegedly fraudulent schemes. The 'justice model' encompasses the moral fabric of our justice system, setting a code of laws and methods of dealing with the need to protect the interest of society as a whole. Protecting society's interest includes a fiduciary duty to protect the funds collected by the government through taxes and fees. The laws discussed above demonstrate that the protection of the people and society in general is of utmost importance to the moral fabric of the United States. The profit maximization theory and justice theory are counterbalancing forces because often times the protection of individual consumers does not run in parallel with capitalism and a company's goal of maximizing profits.

Profit Maximization Theory

Private U.S. companies generally operate by setting prices and output at a level that produces the greatest profit, with the goal of obtaining the greatest profit margins possible given the constraints facing them. Pharmaceutical companies must recover the expenses associated with innovation, marketing, and promotion and also satisfy shareholders by maximizing profits.

At the same time, pharmaceutical companies must follow a labyrinth of rules and regulations that are unique to the pharmaceutical industry. If a pharmaceutical company

follows the profit maximization theory, off-label promotion or price manipulation are attractive activities. If the profits generated from the illegal activity are greater than the repercussions, it makes more sense to maximize profits. The problem with this thought process is in the ramifications of such activities. If fraudulent schemes are used, health care in general costs more, and taxpayers in particular, pay more. The schemes may also threaten the health and safety of consumers.

If the pharmaceutical company follows the profit maximization theory, and no association exists between the repercussions of such schemes and drug sales, then this study will suggest the need for a change in legislation. On the other hand, the associations and trends of this study could demonstrate that the ramifications and regulation already in place work to curb such schemes and bring the government back to the same place they would have been if the illegal scheme had not taken place. In this case, refuting the underlying premise of this study. The study design will allow for either result.

According to the above profit maximization theory, we can expect that drug companies engage in sometimes allegedly illegal activities that enable them to generate higher profit margins. According to the 'justice theory', we can expect that the current regulative and enforcement measures attempt to curb such activity. And finally, depending on which theory predominates, the settlement or verdict amounts should either put the government funded program in the same position they would have been had it not been for the illegal scheme, or fail to economically damage the pharmaceutical company enough to make it cost prohibitive for them to engage in illegal schemes.

3.2 Study Methods and Data Sources

This is an observational study of secondary data to ascertain whether dollars spent on medication or other variables influence settlement amounts. The study focuses on lawsuits involving marketing and promotional schemes (off-label promotion and providing kickbacks to prescribers in exchange for prescribing a certain drug) brought on behalf of the United States government to recover under the False Claims Act and/or Food Drug and Cosmetic Act from 1991 through mid-2010.

The study includes two phases: a qualitative analysis and a quantitative analysis. The qualitative analysis focuses on a thorough literature review of each lawsuit as described in more detail below. The results of the qualitative analysis are summarized on a lawsuit by lawsuit basis in Chapter 4.

The information obtained through qualitative analysis provides the basis for the variables selected for the quantitative phase of the study. I selected non-parametric statistics, specifically the Chi-Square test and the Mantel-Haenzel test to analyze whether any associations between variables and the settlement amount exists. The remaining parts of this Chapter describe the specific methods and data sources used.

The basis for case identification and selection was DOJ Press Releases and HCFAC Annual Reports. The selected cases had at least one drug where allegations involved marketing schemes with a particular emphasis on off-label promotion. All cases selected had to result in a settlement or a final verdict from 1991 through mid-2010.

Twenty-one cases met the above criteria. A search for the civil and/or criminal

case identification number utilized the following methods: I sent a list of information gathered from the DOJ or HCFAC about each lawsuit to Tax Payers Against Fraud who then sent me back a list of civil case identification numbers that corresponded to some of the cases; I searched LexisNexis Legal for all federal cases using drug names as the key word, and identified a few case identification numbers through reading related lawsuits (generally class or derivative actions); I searched the internet for any information that could lead to a civil and/or criminal case identification number. Through these sources, I identified a civil and/or criminal case identification number(s) related to each lawsuit.

I used PACER to find the dockets for each case, and then recorded the lawsuit filing date (the date of the first Complaint). I pulled the most recent, available, and unsealed Complaint. I then compared the asserted facts in the Complaints with the information from the DOJ Press Releases or HCFAC Annual Report to ensure that the Complaint directly related to the settlement. I relied on the Complaints to identify specific factual allegations and used this information for the Case Studies in Chapter 4 and to attempt to identify the approximate timeframes of the alleged illegal marketing or promotional activities. It should be noted that there may be other Complaints relating to the same settlement (i.e., in different Federal district courts or by different whistleblowers), but only certain pleadings were unsealed and available on PACER. It is further noted that once I found one Complaint relating to the case, I did not search for other Complaints filed separately in different jurisdictions.[183]

[183] Some lawsuits included Complaints filed in more than one jurisdiction.

The study includes publicly available information (i.e. settlement or verdict amounts and the drugs involved in the litigation obtained through DOJ Press Releases and Annual Reports) and nonpublic information (i.e. IMS Health data) obtained through an academic Licensing Agreement with IMS Health Incorporated.

The sample size consists of twenty-one lawsuits, and twenty-five drug agents. Of these cases, 16 involve one drug agent, and five involve more than one drug. The case studies summarized within Chapter 4 (Results) describes the information collected from the Complaints and other literature. This information provides the foundation of the study and the basis for the variables chosen for quantitative analysis.

3.2.1 Methods and sources for the dependent variable

I collected the settlement amounts from the DOJ Press Releases and HCFAC Reports. In some cases, the publicly available information did not break down the dollar amounts attributable to each drug, and in these cases, I calculated an adjusted settlement amount. The total settlement amount is the total settlement amount as reported by the Department of Justice Press Release. A total settlement "adjustment" was necessary where the total settlement included multiple drugs. The following drugs required an adjustment: Actiq, Gabitril, Provigil; Intron-A and Temodar; Celexa and Lexapro; Abilify; Bextra.

The total settlement amount for the lawsuit involving Actiq, Gabitril, and Provigil was approximately $ 313,000,000. The total settlement amount for the lawsuit involving Intron-A and Temodar was approximately $ 435,000,000. The total settlement amount for the lawsuit involving Celexa, Levothroid, and Lexapro was approximately $

425,000,000. For these settlements, the amounts allocated to each drug were calculated by using the proportion of Medicaid dollars for each drug.[184] The following equation was used to calculate the adjusted settlement amount.

Adjusted settlement amount =

[(total Medicaid dollars for one of the drugs pre-settlement) / total Medicaid dollars pre-settlement for each of the drugs] * total settlement amount

A similar adjustment was calculated for Abilify because multiple other drugs and violations were included in the government's settlement with Bristol-Myers Squibb and there was no publicly available information concerning the amount of the total settlement attributable to Abilify. With over 50 drugs included in the lawsuit, every drug for which Bristol-Myers Squibb was reimbursed from 1998 through the month prior to settlement was collected from CMS for a total Medicaid total dollar amount. The total dollar amount for Ability was then divided by the total dollar amount for all drugs collected (over 50 drugs) to generate a percent of total sales for each product. The percent of total sales relative to all prescription Bristol-Myers Squibb pharmaceuticals was multiplied by the total settlement amount of $515,000,000 resulting in an adjusted settlement amount of $ 93,166,690. The $93,166,690 amount was added to the 4 million dollar settlement

[184] The decision to use Total Medicaid dollars for the adjusted settlement amount was based on a conversation with Steve W. Schondelmeyer on November 21, 2012.

amount incurred by Ostuka Pharmaceuticals for its part in the off-label promotion of Abilify.

The Bextra settlement adjustment was based solely upon information available that identified the amount allocated for each drug involved in the settlement.

3.2.2 Methods and Sources for the independent variables

Nominal Variables

After identifying each drug, I collected data from the FDA's website. **Table A** shows the information identified and collected from the FDA's website. I collected the following information from the FDA's website: the number of indications as of 2009 for each drug (identified as "Indications" in Table A), the quantity, if any, of FDA Warning Letters associated with each drug from DDMAC (identified as "Warning" in Table A), information on Black Box warnings (identified as "BBStatus" in Table A), and whether the Black Box warning was for a use alleged to be promoted off-label based on the allegations stated in the Complaints or DOJ Press Releases (identified as "BBPromo" in Table A). **Tables B-1** and **B-2** include other information collected but not used for the quantitative analysis.

Off-Label and Non-Evidence Based Use

I used two data sources to identify off-label uses and non-evidence based uses for each drug. First, the FDA approved indications for each drug and available clinical efficacy and safety evidence for off-label uses for each drug were identified using the American Hospital Formulary System Drug Information. Second, IMS National Disease

and Therapeutics Index identified specific uses as reported by prescribers. The following paragraphs describe both sources in more detail.

American Hospital Formulary System Drug Information (AHFS DI®)[185]

AHFS DI® is the longest published federally designated drug compendium issued by a scientific and professional society. The American Society of Health-System Pharmacists publishes a hard copy text of the AHFS DI once a year. The AHFS DI® is evidence-based and peer-reviewed, compiled without the influence of manufacturers, insurers, regulators, or other interested parties.

AHFS DI® contains information from medical literature and expert advice from over 500 medical scientists, physicians, pharmacists, pharmacologists, and other professionally qualified individuals that goes beyond FDA-approved labeling. The compendia includes information on the following:

- Information on prescription, OTC, ophthalmic, and dermatologic drugs, plus vitamins and immunizing agents
- Extensive off-label uses and dosing options
- Expanded and revised content, with many new monographs
- Therapeutic recommendations supported by evidence from primary research
- Pharmacology and Pharmacokinetics
- Preparations, Chemistry and Stability

[185] The statements, findings, conclusions, views, and opinions contained and expressed herein are not necessarily those of the contributors and publishers of American Hospital Formulary System Drug Information Incorporated or any of its affiliated or subsidiary entities.

- Interactions, Adverse Reactions, Cautions, and Toxicity…among many more!

Monographs include: drug interactions; adverse reactions; cautions and toxicity; therapeutic perspective; specific dosage and administration information; preparations, chemistry, and stability; pharmacology and pharmacokinetics; contraindications; and more.

The information collected from AHFS DI® is available upon request , but is too large to include as an Appendix to this dissertation. A third year pharmacy student collected information on all uses as designated in the compendium and put the data into large excel spreadsheets. The collection included all data on uses in AHFS for each drug per year from 1991 to 2009.

The second data source used for identifying off-label uses was the IMS National Disease and Therapeutic Index.

IMS National Disease and Therapeutic Index™ (NDTI)[186]

IMS provided quarterly data from its NDTI database from 1998 to 2009 for the 27 drug products. The NDTI data collects physician prescribing patterns and treatment of disease. For each patient seen during a consecutive two-day period each calendar quarter, participating physicians complete an encounter form that includes information

[186] The statements, findings, conclusions, views, and opinions contained and expressed in this dissertation are based in part on data obtained under license from the following IMS Health Incorporated information service(s): National Disease and Therapeutic Index™ (January 1998 through December 2009), Integrated Promotional Services ™ (January 2003 through December 2009), National Sales Perspectives ™ (January 1998 through December 2009). All Rights Reserved. The statements, findings, conclusions, views, and opinions contained and expressed herein are not necessarily those of IMS Health Incorporated or any of its affiliated or subsidiary entities.

about diagnoses and drug therapies. Each record of a drug therapy within the NDTI is linked to a specific six-digit taxonomic code capturing diagnostic information similar to the International Classification of Disease 9th Revision (ICD-9).

The American Medical Association and the American Osteopathic Association provide a master list of physicians from which IMS selects a representative sample stratified by geographic region and specialty. The NDTI sample is drawn from office based physicians. The data elements included product (brands only), prescriber specialty, diagnosis 6, and drug uses.

NDTI uses a two-stage stratified cluster, randomly drawn. In the first stage, NDTI randomly selects physicians from the described universe of physicians. The final NDTI sample consists of a nationally representative sample of over 4,300 office-based physicians in the United States.

During the second stage, NDTI randomly assigns a start day to report data for two consecutive workdays per quarter, thus individual physicians do not collect information every month. Reporting days are randomly assigned to ensure that all workdays in a report period are covered. Saturdays, Sundays and holidays are assigned as reporting days to physicians who practice on those days. For instance, in 2010, 1,380 physicians recoded data for 2,760 workdays each month, and 4,140 physicians recorded data for 8,280 workdays each quarter.

Using the NDTI data source, I reviewed each use and designated a “1” for indicated uses based on information collected from the AHFS and a “0” for non-indicated uses. These categories represent the off-label status for each drug, by quarter.

The off-label uses designated as evidence-based according to the AHFS were designated as follows: “1” for indicated uses; “3” for off-label uses with clinical efficacy evidence according to the AHFS; “4” for off-label uses that are non-evidence based uses. No information for Genotropin or Serostim was available in the AHFS data source so DrugDex by Micromedix was used to collect information on off-label uses and indications for Genotropin and Serostim. The information on categories were manually entered into an excel workbook. Once complete, the categorization per use per year extracted from an excel worksheet using SAS. Within SAS, the uses for each drug were rolled up into totals. **Table C** includes the off-label uses as categorized for each drug and the ratio of off-label uses relative to all uses for each drug.

No information was available for Protropin through the NDTI data source, and thus Protropin was excluded. Limited information was available on Actimmune from NDTI, but all available uses were for the treatment of pulmonary fibrosis, which was designated a “0” for not indicated and “4” for off-label use where there was insufficient evidence to support using the drug for this use according to AHFS. The off-label use rate identified in **Table C** was calculated by taking the number of off-label uses (“Reg0”) divided by the total of all uses for the drug.

Table D includes the non-evidence based use totals as categorized for each drug and the ratio of non-evidence based use relative to all uses for each drug. The non-evidence based rate identified in **Table D** was calculated by taking the number of off-label uses without sufficient evidence of efficacy (“NoEvid3”) divided by the total of all

uses for the drug. One category of uses within the NDTI database were designated as "information not available." These "uses" were given a "6" as shown in **Tables C** and **D**.

Dollars and Units

I used two data sources for dollars and units per drug. First, IMS total dollars and units from IMS National Sales Perspective™. Second, Medicaid total dollars and units from Centers for Medicaid and Medicare Services. The following paragraphs described both sources in more detail.

IMS National Sales Perspectives™ (NSP)[187]

IMS provided monthly sales data from 1998 to 2009 from its National Sales Perspectives™ (NSP) database for the 24 drug products. NSP is the industry standard for measuring pharmaceutical sales at actual transaction prices — rather than average wholesale price or dollarized prescriptions. NSP monitors every major class of trade and channel of distribution for prescription pharmaceuticals, over-the-counter products and select, self-administered diagnostic products in the United States, measuring volume of dollars and units moving from manufacturers into various outlets within all 50 states.

Derived from the processing of more than 1.5 billion transactions each month, channel coverage includes retail (chain/mass merchandisers, independent and food store pharmacies), non-retail, mail service, non-federal hospitals, clinics, long-term care

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facilities, federal facilities, miscellaneous channels (prisons, universities, etc.), home health care, and HMOs. The specific data elements included channel, product (brands only), product form, product strength, total sales dollars, and total quantity (units). The metrics included were total sales dollars and total quantity per month. IMS Health's National Sales Perspectives™ database was chosen over the National Prescription Audit™ database because the National Prescription Audit™ database only includes three channels of distribution.

The total dollars and total units per month for each drug were extracted from the excel spreadsheets provided by IMS into SAS. Within SAS, the total pre-settlement totals were summed into one value. The pre-settlement amount is the amount from the time the drug entered the market to the month before the date the lawsuit settled.

For the missing quarters, data available for the last quarter (fourth quarter of 2009) was inputted for all subsequent quarters ending at the month prior to settlement. Where the pre-settlement period ended in the middle of a quarter, the calculation made depended upon the relevant month within the quarter. For instance, if the pre-settlement ended in May 2007, data for the second quarter of 2007 divided by 2/3. The drugs analyzed that required an input were Lexapro (from 1Q 2010 through the first two months of 3Q 2010), TOBI (first month of 2Q 2010), and Seroquel (1Q 2010). Although the lawsuit involving Celexa settled in 2010, it was not necessary to compute data for Celexa since dollars and units were negligible far in advance of 2009 because Celexa went off patent and became commercially available through other manufacturers by 4Q 2004. Similarly, other manufacturers began selling Topamax in 2Q 2009.

Medicaid units and dollars

The second data source used for the Medicaid data is the Centers for Medicaid and Medicare Services through its Medicaid Drug Rebate Program Data files. Rebates are not included within the files so the total dollars are higher than the actual amount paid by the states to the company for the drug product. The files contain the active drugs that have been reported by participating drug manufacturers as of the most recent rebate reporting period under the Medicaid Drug Rebate Program. In this case, data was available through the second quarter of 2009. All drugs are identified by National Drug Code (NDC), unit type, units per package size, product name, Food and Drug Administration (FDA) approval date, the date the drug entered the market, plus indicators to show whether the drug is an innovator or non-innovator drug; whether it is available by prescription or over-the-counter (OTC); the FDA therapeutic equivalency code; and the Drug Efficacy Study Implementation (DESI) rating and termination date, if applicable.

Using NDC codes identified for each of the 25 drug products, the Medicaid data was extracted from excel spreadsheets created through the PRIME Institute based on the Medicaid Drug Rebate Program Data files. The Medicaid data was only available through second quarter of 2009. For subsequent quarters, data was inputted in the same way described above for IMS dollars and units. The drugs analyzed that required an input were Lexapro (from 2Q 2009 through the first two months of 3Q 2010), Cardizem LA (from 2Q 2009 through 3Q 2009), TOBI (from 2Q 2009 through the first month of 2Q 2010), and Seroquel (from 2Q 2009 through 1Q 2010).

Promotional Dollars

Lastly, I used IMS Integrated Promotional Services™ to collect data on promotional dollars spent on each drug.

IMS Integrated Promotional Services ™ (IPS)[188]

IMS provided quarterly data from its IPS database from 2003 to 2009 for 25 drug products. The IPS data collects the amount a given manufacturer spends per drug by type of promotion. The metric was total promotional dollars (total spend), which includes professional promotion (professional journal advertising spend and sales representative details) and direct consumer advertising, if applicable. Professional promotion includes office and hospital promotion and journal advertising. Office promotion includes costs associated with sales activities of pharmaceutical representatives that are directed to office-based physicians. Hospital promotion captures the costs associated with sales activities of pharmaceutical representatives that re directed to hospital-based physicians and directors of pharmacies. Journal advertising reflects advertising expenditures for prescription products appearing in medical journals.

The total promotional dollars per quarter for each drug were extracted from the excel spreadsheets provided by IMS into SAS. Within SAS, the total pre-settlement

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totals were summed into one value. The pre-settlement amount is the amount from the time the drug entered the market to the month before the month the lawsuit settled.

3.2.3 Categorization of each Variable

Due to the statistical tests selected for analysis, I created two categories for each variable based on the distribution of values within each variable. For example, **Figure I** shows the distribution of the dependent variable, settlement amount. The dotted line shows the cut-off for categorizing the variable into a high group and a low group. Rather than creating the groups evenly to reflect 12 values in each of the two groups, I selected the groups based on distribution of the variable. As shown in **Figure I**, there was a greater difference between the settlement amount for Celexa and Abilify compared to Celexa and Gabitril. As a result, I included 13 values in the "high group" and 11 values in the "low group." I used the same method to categorize the independent variables based on their distribution. **Table E** provides a summary of each continuous variable with measurement information and the source and the operation. **Table E-2** provides a schematic of the independent variables and dependent variable. The following paragraphs identifies the categories per variable. The following figure and table show the distribution of the dependent variable, total settlement amount. The settlement amount was measured as a continuous variable in two categories: < 100 million and 100 million plus.

Figure Ia: Settlement Amounts

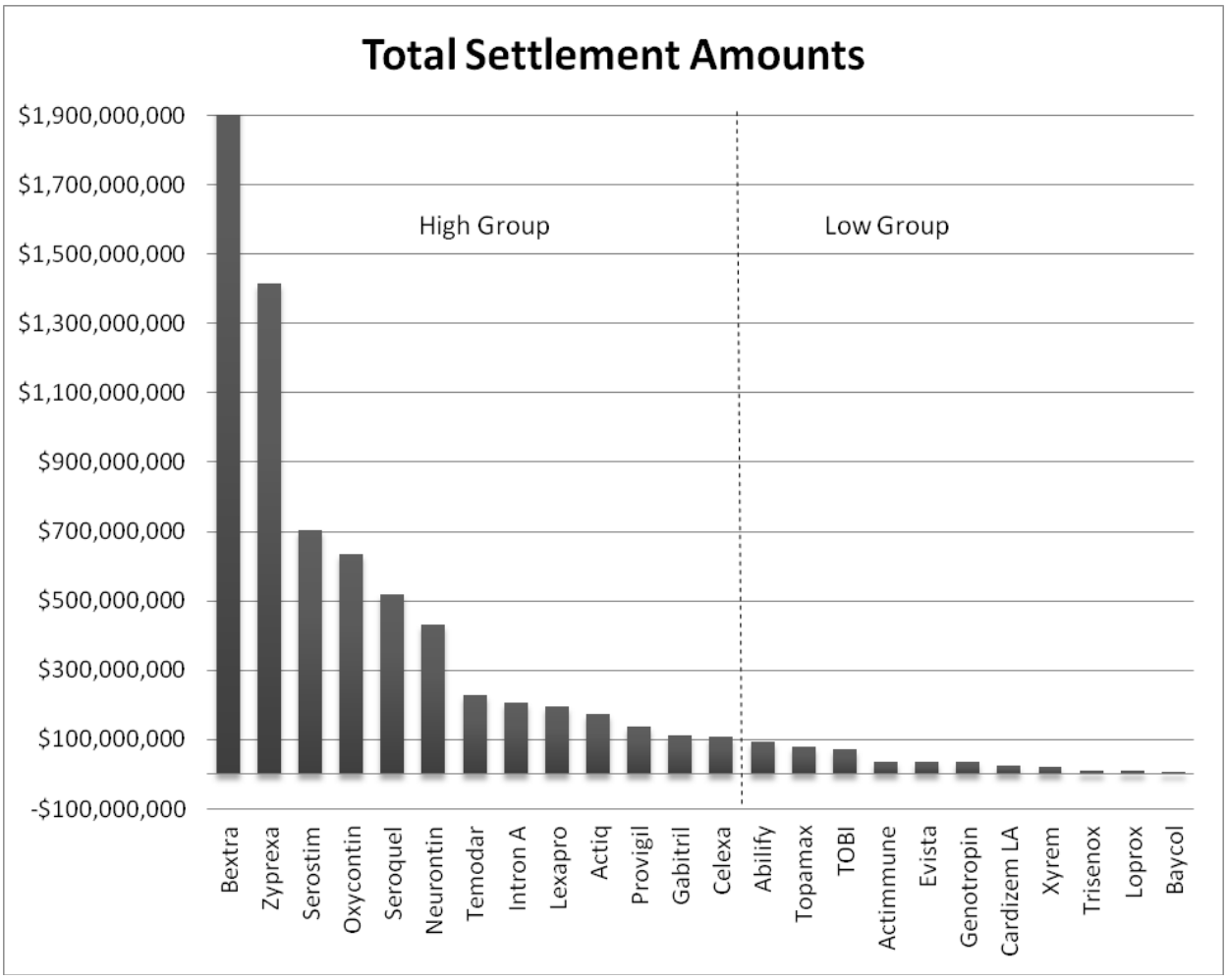

Figure Ib: Settlement Amounts

DrugName	AdjTotSettle
Bextra	2,300,000,000
Zyprexa	1,415,000,000
Serostim	704,000,000
Oxycontin	634,515,475
Seroquel	520,000,000
Neurontin	430,000,000
Temodar	228,906,613
Intron A	206,093,387
Lexapro	194,445,117
Actiq	175,656,582
Provigil	137,506,971
Gabitril	111,836,447
Celexa	108,983,643
Abilify	93,166,690
Topamax	81,000,000
TOBI	72,500,000
Actimmune	36,900,000
Evista	36,000,000
Genotropin	34,680,000
Cardizem LA	24,600,000
Xyrem	20,000,000
Trisenox	10,500,000
Loprox	9,800,000
Baycol	8,000,000

I selected the independent variables based on available factors collected through qualitative analysis that may have an impact on the settlement amount.

Total IMS Dollars ("TotalDollars"): measured as a continuous variable in two categories:

< 1.5 Billion and 1.5 Billion +

Total Medicaid Dollars ("medDol"): measured as a continuous variable in two categories:

<500 million and 500 million +

Total IMS Units ("Units"): measured as a continuous variable in two categories:

<500 million and 500 million+

Total Medicaid Units ("medUnits"): measured as a continuous variable in two categories:

<100 million and 100 million+

Promotional Dollars ("PromoDollars"): measured as a continuous variable in two categories:

<50 million and 50 million+

Off label uses relative to all uses ("NdtiOffRegRate"): measured as a continuous variable in two categories:

<0.7 and 0.7+

Non-evidence based uses relative to all uses ("NdtiNonClinicalRate" or "NoEvidenceRate"): measured as a continuous variable in two categories:

<0.4 and 0.4+

Estimated promotional dollars allocated to non-evidence based use ("PromoDolClin"): measured as a continuous variable in two categories:

<100 million and 100 million+

Estimated promotional dollars allocated to off-label use ("PromoDolOff"): measured as a continuous variable in two categories:

<50 million and 50 million+

Estimated Medicaid units allocated to off-label use ("MedUnitOff"): measured as a continuous variable in two categories:

<35 million and 35 million+

Estimated Medicaid dollars allocated to off-label use ("MedDolOff"): measured as a continuous variable in two categories:

<155 million and 155 million+

Estimated Medicaid units allocated to non-evidence based use ("MedUnitClin"): measured as a continuous variable in two categories:

<50 million and 50 million+

Estimated Medicaid dollars allocated to non-evidence based use ("MedDolClin"): measured as a continuous variable in two categories:

<140 million and 140 million+

Estimated IMS units allocated to off-label use ("UnitOff"): measured as a continuous variable in two categories:

<400 million and 400 million+

Estimated IMS dollars allocated to off-label use ("TotDolOff"): measured as a continuous variable in two categories:

<2 Billion and 2 Billion+

Estimated IMS units allocated to non-evidence based use ("UnitClin"): measured as a continuous variable in two categories:

<400 million and 400 million+

Estimated IMS dollars allocated to non-evidence based use ("TotDolClin"):

measured as a continuous variable in two categories:

<1 Billion and 2 Billion+

Black box status ("BBStatus"): measured as a nominal variable in two categories:

No black box warning on the label = 0

black box warning on the label = 1

Black box warning associated with a use alleged promoted off-label ("BBstatus"):

measured as a nominal variable in two categories:

No black box warning associated with off-label use = 0

Black box warning associated with off-label use = 1

FDA Warning Letter ("Warning"): measured as a nominal variable in two categories:

No FDA Warning Letters = 0

One or more FDA Warning Letters = 1

Number of indications ("Indications"): measured as a nominal variable in three categories:

One indicated use= 1

Two to three indicated uses= 2-3

Four or more indicated uses= 4+

3.3 Quantitative Analysis

I analyzed the available data for each variable with the Chi-Square test and Mantel-Haenszel tests to test the hypotheses. I chose these statistical tests based on an assessment of the ability to meet both the explicit and implicit underlying assumptions of

each. The two statistical tests were chosen based on the following considerations: manner in which the sample was drawn, the nature of the population from which the sample was drawn, the types of measures or scaling which were employed in the operational definitions of the variables used, the size of the sample, and the assumptions inherent to the population from which the sample was drawn.

Parametric tests are the most powerful statistical tests, but they require the most extensive assumptions and more data. At a minimum, the following conditions must be met before confidence can be placed in a probability statement obtained from a parametric test:

1) independence of observations (the selection of any one case from the population of inclusion for the sample must not bias the chances for selection of any other cases; likewise, the score obtained from that case must not bias the score of any other case);
2) normal distribution;
3) homogeneity of variance;
4) measurement minimally at the interval level.

When one or more of the assumptions of the statistical model are absent, the probability statements concerning the hypotheses in question may be rendered meaningless even though a statistic can be calculated. Although empirical evidence suggests that slight deviations in meeting the underlying assumptions of a test will not have radical effects on the probability levels (i.e., that the tests are in fact robust),

disagreements exist as to what constitutes "slight deviations."[189] The question is whether the assumptions are "bent" which would still allow for the legitimate use of parametric tests, or "broken" rendering any derived probability statements from parametric tests meaningless.

In consideration of the above assumptions and the research questions, it was determined that non-parametric tests, specifically the Chi-square and Mantel-Haenszel tests best met the needs of this research. The greatest underlying concern was the sample size of the dataset and the abnormal distribution of variables. There is little support for using parametric tests considering the size and distribution within variables. As a result, this research employs non-parametric tests.

3.3.1 The Chi-Square Test

The most common non-parametric test of association is the Chi-square (X^2). When the data collected consists of frequencies in discrete categories, X^2 is used to determine if significant differences between two (or more) independent groups exists. The underlying measurement may be as weak as nominal scaling.[190]

The hypothesis subjected to testing is that two groups differ with respect to some characteristic. This is assessed by an examination of the relative frequencies with which group members fall into the specific category designated by the research design and the frequencies which might have been expected had no differences between the groups existed.

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[189] SIEGEL, S. NONPARAMETRIC STATISTICS FOR THE BEHAVIORAL SCIENCES, NEW YORK:MCGRAW AND HILL (1956) at p. 20.
[190] SIEGEL, 1956; NORMAN G.R. AND STREINER, D.L. PDQ STATISTICS. TORONTO AND PHILADELPHIA: B.C. DECKER, INC. (1986).

The X^2 statistic is of the form:

$$\chi_c^2 = \sum \frac{(O_i - E_i)^2}{E_i}$$

and is distributed as X^2 with df = (r-1)(c-1) if H_o is true.

The two most basic requirements are that there is independence among the separate measures, and that the theoretical frequencies resemble a reasonable size. If the expected frequencies in each cell are smaller than minimal, the use of X^2 may not be meaningful. Exactly what constitutes reasonable size, however, has been the subject of much debate. In general, researchers most commonly follow Cochran's suggested rule: when N > 20, it is appropriate to utilize the X^2 test if all expected frequencies are 5 or more. If the smallest expected frequency is less than 5 in 20% or more of the cells, the researcher may turn to the Fisher Exact Test. Some researchers have suggested that Cochran's rule is too stringent and that expected values may be as low as unity without affecting the results of the test. Others state that in the majority of cases the Chi-square criterion may be used in tables where the expected values need only exceed 0.5 in the smallest cell.[191]

[191] EVERITT, B.S., THE ANALYSIS OF CONTINGENCY TABLES, LONDON: CHAPMAN AND HALL, LTD. (1977) at p. 40.

3.3.2 Mantel-Haenszel Chi-Square Test

Nathan Mantel and William Haenszel first proposed this modified Chi-square test in 1959 as a means of analyzing data from retrospective studies of disease incidence.[192] It is one of several designed to examine the relationship among a number of independent variables and a single counted dependent variable. The Mantel-Henszel (M-H) test may be applied to data if each of several comparisons in a study are conceptualized as falling into a 2 x 2 contingency table form.

In one sense the M-H is the non-parametric equivalent of analysis of covariance (ANCOVA) in that it has been employed to correct for bias caused by different numbers of cases in subgroups, to improve sensitivity of an overall Chi-square, and to investigate the interactions between factors. Unlike ANCOVA, however, the M-H is limited to two independent variables.

Being a variation of the Chi-square test, the test statistics for the M-H Test resembles the familiar X^2 statistic and is of the form:

$$\textbf{M-H } X^2 = \frac{(\sum \text{a's} - \sum a_e\text{'s})^2}{\sum \text{variances}}$$

and distributed as X^2 with df = 1 if H_o is true.

The M-H focuses on the upper left cell of a contingency table comprised of the dependent variable under study and two independent variables. By convention this cell is

[192] Mantel, N. and Haenszel W., Statistical aspects of the analysis of data from retrospective studies of disease. J. Am. Pharma. Assoc. (1963).

designated “a.” A subtable of the original table is conceptualized and a determination of the expected value of “a” if there were no association between the two independent variables under consideration is made. From this expected value, the variance of the estimate is determined. This process repeats for all subtables generated from the larger contingency table. The a’s are then summed. If there is no association, the sum of these a’s should be normally distributed with a mean equal to the sum of the expected values, and a variance equal to the sum of the variances. The resulting test statistic (designated above) is then associated with a probability in the usual manner.

This study utilizes the M-H to examine the relationship between selected independent variables of interest and the dependent variable, adjusted settlement amount, as a test of covariation. M-H allows for this analysis without conducting repeated statistical tests of 2 x 2 contingency tables and any subsequent violation of degrees of freedom rules.

The following chapter presents the results of the qualitative analysis and statistical analysis based upon the methods and sources described above.

CHAPTER 4
RESULTS

Qualitative study findings

4.1 Individual Case Reviews

The results below describe the publicly available information retrieved about each lawsuit. The summaries include three categories: (1) overview of the lawsuit; (2) clinical information, particularly the FDA indications for each drug; and (3) information about the settlement and investigation using the Complaints, DOJ Press Releases, HCFAC reports and other literature discussing the settlement. The depth of information varies depending upon what is publicly available about each lawsuit and the drugs involved. It is important to note that most of the factual allegations discussed below originate from the Complaints, but the respective pharmaceutical company did not necessarily admit to the allegations unless indicated. In other words, the civil settlements generally involve money provided to the government from the pharmaceutical company in exchange for the government dropping the lawsuit, but admitting guilt associated with the government's allegations, regardless of whatever payment the company agrees to provide the government, is not required.

4.1.1 Protropin®—Genentech

Overview

The DOJ announced the first off-label marketing settlement on April 14, 1999.[193] The settlement involved allegations that Genentech illegally promoted its first FDA-

[193] Janet Rae-Dupree, *Putting a Mistake Behind It, Genentech Pays a $50 Million Fine*, Business Week (Apr. 15, 1999), available at http://www.businessweek.com/bwdaily/dnflash/apr1999/nf90415c.htm.

approved product, Protropin (Somatrem).[194] Genentech agreed to pay a $50 million fine and to plead guilty to criminal charges that it promoted Somatrem as a useful treatment for conditions not approved by the FDA.[195]

Clinical

The FDA approved Somatrem on October 17, 1985 for children with a rare form of dwarfism caused by lack of a natural growth hormone. The AHFS never published indications or use information for Somatrem.

Factual Allegations & Admissions

The FDA investigation began in 1995 when suspicions arose that Genentech was pushing the drug as a way "to help healthy, but short, children grow taller."[196]

Drug sales and stock price implications

The drug accumulated sales of $1.2 billion between 1985 and 1995. The drug sold $214 million in 1998.[197] The government agreed that the illegal marketing activities stopped in 1994.[198]

4.1.2 Neurontin®—Pfizer I (Warner–Lambert, Parke-Davis)

Overview

On May 13, 2004, the DOJ announced the second off-label settlement of its kind against a pharmaceutical company. Warner-Lambert agreed to plead guilty to two counts

[194] *Id.*
[195] *Id.*
[196] *Id.*
[197] *Id.*
[198] *Id.*

of violating the FDCA, agreed to settle its federal civil FCA liabilities, and to settle other civil liabilities connected to Warner Lambert's Parke-Davis divisions' fraudulent drug promotion and marketing tactics involving Neurontin.[199] Both companies are now subsidiaries of Pfizer, but the illegal conduct occurred prior to Pfizer's acquisition (June 2000) of Warner-Lambert.[200]

Pfizer paid more than $430 million dollars to resolve criminal charges and civil liabilities.[201] According to the Press Release, the company promoted Neurontin for the treatment of bipolar mental disorder, various pain disorders, amyotrophic lateral sclerosis (ALS, a degenerative nerve disease commonly referred to as Lou Gehrig's disease), attention deficit disorder, migraine, drug and alcohol withdrawal seizures, restless leg syndrome, and as a first-line monotherapy treatment for epilepsy (using Neurontin alone, rather than in addition to another drug).[202] "Warner-Lambert promoted Neurontin even when scientific studies had shown it was not effective."[203]

The settlement included the following components:

> (a) Warner-Lambert has agreed to plead guilty to two counts of violating the Food, Drug & Cosmetic Act with regard to its misbranding of Neurontin by failing to provide adequate directions for use and by introduction into interstate commerce of an unapproved new drug. Warner-Lambert has, as punishment for these offenses, agreed to pay a $240 million criminal fine, the second largest criminal fine ever imposed

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[199] Press Release, Department of Justice, *Warner-Lambert to pay $430 Million to Resolve Criminal & Civil Health Care Liability Relating to Off-Label Promotion* (May 13, 2004)[hereinafter Off-Label Promotion].
[200] *Id*.
[201] *Id.* at 4.
[202] *Id*.
[203] *Id*. at 4.

in a health care fraud prosecution. The Plea Agreement between the United States and Warner-Lambert specifically states that Warner-Lambert's criminal conduct caused losses of $150 million and that the violations are felonies as a consequence of Warner-Lambert's prior Food, Drug & Cosmetic Act conviction.

(b)Warner-Lambert has agreed to settle its federal civil False Claims Act liabilities and to pay the United States $83.6 million, plus interest, in civil damages for losses suffered by the federal portion of the Medicaid program as a result of Warner-Lambert's fraudulent drug promotion and marketing misconduct.

(c)Warner-Lambert has agreed to settle its civil liabilities to the fifty states and the District of Columbia in an amount of $68.4 million, plus interest, for losses the state Medicaid programs suffered as a result of Warner-Lambert's fraudulent drug promotion and marketing misconduct.

(d) Warner-Lambert has agreed to settle its civil liabilities to the fifty states and the District of Columbia in an amount of $38 million, plus interest, for harm caused to consumers and to fund a remediation program to address the effects of Warner-Lambert's improper marketing scheme. This part of the global settlement agreement was negotiated by the Consumer Protection divisions of the fifty State Attorneys General.

(e) Pfizer Inc, Warner-Lambert's parent company, has agreed to comply with the terms of a corporate compliance program, which will ensure that the changes Pfizer Inc made after acquiring Warner-Lambert in June 2000, are effective in training and supervising its marketing and sales staff, and ensures that any future off-label marketing conduct is detected and corrected on a timely basis. In addition, Warner-Lambert agreed to an injunction by a state court against continuing the improper conduct that was the subject of the States' Consumer Protection Divisions investigation. [204]

Clinical

The FDA approved Neurontin (gabapentin) on December 30, 1993 after a two-year review by the FDA.[205] Neurontin (gabapentin) received approval for the indications

[204] *Id*.

[205] Orange Book, fda.gov, approved December 30, 1993 in 100, 300 and 400 mg capsules. On October 9, 1998, the FDA approved the 600 and 800 mg capsules.

of adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults with epilepsy.[206] A list of the indications and off-label uses per drug as published in the AHFS from 1997 through 2010 is available upon request.

Gabapentin is an amino acid structurally-related to the inhibitory neurotransmitter gamma-aminobutyric acid (GABA); however, its antiepileptic activity appears unrelated to any direct effects on the GABA system.[207] Although the drug received a priority review by the FDA, safety concerns in rat studies prompted a more thorough safety review by the agency.[208]

Once approved the medication became a huge success for Warner-Lambert as demonstrated by the billions of dollars in sales generated from the product. As stated earlier, gabapentin is in a class of agents commonly prescribed off-label, but the frequency of gabapentin prescribing was even alarming to researchers. Of the anticonvulsants, antidepressants, and antipsychotic agents researched in one study, gabapentin (considered an anticonvulsant) was the most frequently prescribed off-label.[209]

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[206] Micromedex® Healthcare Series, DRUGDEX® Evaluations, Neurontin drug profile.
[207] Micromedex® Healthcare Series, DRUGDEX® Evaluations, Neurontin drug profile.
[208] The Pink Sheet. *Warner-Lambert's Neurontin Approved for Adjunctive Therapy in Epilepsy Patients*, 56(001) FDC Report, 11 (Jan. 3 1994).
[209] In 2001, 98.04% of Medicaid patients using gabapentin in Georgia, were being treated for something other than the two indications (partial epilepsy or postherpetic neuralgia). Also, the probability of receiving a drug off-label was much higher for patients 65 years or older compared to those under 65 years old. "The elderly are a group of patients in whom drug effects are influenced by age-related changes in pharmacokinetics, pharmacodynamics, and homeostasis, which render them more susceptible to adverse drug reactions." "Since the risk/benefit rations of most off-label uses are uncertain, using drugs in accordance with evidence to support benefit should be especially stressed among the senior population." *See* Chen H., et al., *Off-label Use of Antidepressant,*

In a study using the 2001 IMS Health National Disease and Therapeutic Index (NDTI), researchers found that off-label use was most common among cardiac medications (46%) and anticonvulsants (46%).[210] Out of the individual medications, gabapentin (83%) and amitriptylline hydrochloride (81%) were most frequently used off-label. Perhaps the most alarming conclusion was that for all drugs, including gabapentin, "[n]o more than 30% of the off-label practices observed were supported by strong scientific evidence."[211]

As of May 2010, gabapentin has been approved for the following indications: (1) adjunctive therapy in the treatment of partial seizures with and without secondary generalization in epileptic patients older than 12 years of age, and as adjunctive therapy in the treatment of partial seizures in patients 3 to 12 years of age; (2) for the treatment of postherpetic neuralgia in adults.[212]

Anticonvulsant, and Antipsychotic Medications Among Georgia Medicaid Enrollees in 2001. 67(6) J Clin Psychiatry, 972, 977, 980 (June 2006).

[210] David C Radley, Stan N. Finkelstein, Randall S Stafford. *Off-label prescribing among office-based physicians.* 166(9) Archives of Internal Medicine, 1021-1026 (2006).

[211] Mack, A., *Examination of the Evidence for Off-Label Use of Gabapentin* 9:6 JMCP (Nov/Dec 2003) at 559 (stating that in the majority of circumstances where it has reported potential for "off-label" use, gabapentin is not the optimal treatment). In another study, researchers found that only 19% to 57% of anticonvulsant off-label uses had evidentiary support from randomized, controlled trials. Chen H., et al. *An epidemiological investigation of off-label anticonvulsant drug use in the Georgia Medicaid population,* 14 J Pharmacoepidemiol Drug Saf 629-638 (2005).

[212] MICROMEDEX® Healthcare Series, DRUGDEX® Evaluations, Neurontin drug profile.

Off-label prescribing is very common for recipients of the second-generation antidepressants, anti-convulsant (i.e. Neurontin®), and antipsychotic agents.[213]

Factual Allegations & Admissions

A former employee of Parke-Davis Division of Warner-Lambert brought the lawsuit against his former company.[214] According to the Complaint, Parke-Davis "formed a scheme to increase the sales of gabapentin while avoiding the substantial expense and delay of petitioning the FDA for approval of expanded or additional uses of gabapentin."[215] The Complaint lists several off-label uses in particular: pain control, mono-therapy for seizures using extremely high doses, control of bi-polar disorder, attention deficit disorder, and other diseases and conditions.[216]

The complaint alleges that after FDA approval, Parke-Davis formed a scheme to increase sales of gabapentin.[217] The allegations included the following, among other things:

a. Illegal kickbacks to physicians who prescribed large amounts of gabapentin for "off-label" purposes to patients whose prescriptions were paid for by Medicare or Medicaid;
b. The formation of a nationwide network of employees falsely referred to as "medical liaisons" whose actual assigned duties consisted entirely of conventional direct sales activities and which did not include any legitimate scientific activity;
c. The illegal direct solicitation of physicians for off-label uses;

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[213] 40% to 70% of recipients receive these agents for off-label purposes. *See* Chen H., et al. *Off-label Use of Antidepressant, Anticonvulsant, and Antipsychotic Medications Among Georgia Medicaid Enrollees in 2001*. 67(6) J Clin Psychiatry, 972 (June 2006).
[214] David Franklin was a former employee of the company. Complaint United States of America ex. rel. David Franklin v. Parke-Davis, division of Warner-Lambert Co., ¶ 1 (No. 96-cv-11651)(Aug. 13 1996).
[215] *Id.* ¶ 8.
[216] *Id.*
[217] *Id.* ¶ 8.

d. The making of false statements to physicians and pharmacists concerning the efficacy and safety of gabapentin for off-label uses;
e. The charging of full price for drugs actually being used in experimental trials and thus subject to federal price restrictions;
f. The systematic avoidance of filing requirements with the FDA;
g. The deliberate avoidance of the FDA's classification of gabapentin as to its therapeutic equivalency and thus the avoidance of Medicare and Medicaid price limitations based on therapeutic equivalency;
h. The use of active concealment to avoid the FDA's enforcement mechanisms and the resultant mandatory interruption of Medicare and Medicaid payments for gabapentin prescriptions;
i. The use of active concealment to avoid the "formulary" policies of various state agencies administering Medicare and Medicaid programs and which are intended to refuse payment for uses of drugs which are not medically recognized as statutorily defined;
j. The payment or offering of gratuities to Parke-Davis employees in order to procure their silence;
k. The active training of Parke-Davis employees in methods of avoiding detection of their activities by the FDA.[218]

According to the Department of Justice, Warner-Lambert's strategic marketing plans and other evidence showed that Warner-Lambert used aggressive marketing tactics to encourage prescribing of gabapentin for a wide variety of unapproved conditions.[219] Associate Attorney General Robert McCallumm, in speaking about the gabapentin settlement, said that "[i]t is of paramount importance that the Department of Justice use every legal tool at its disposal to assure the health and safety of the consumers of America's health care system, and to pursue companies and individuals that steal from the taxpayers and inflict suffering on patients and families."[220]

Besides the financial implications, Warner-Lambert's promotion of gabapentin also created safety concerns. Among the charges against Warner-Lambert was the fact

[218] *Id.* ¶ 9.
[219] Off-label Promotion.
[220] Off-Label Promotion at 4.

that gabapentin was marketed for uses that were proven to be ineffective.[221] The company promoted the drug as a mono-therapy for epileptic seizures even when the FDA rejected this indication.[222] In other words, due to aggressive marketing by Warner-Lambert, some patients received a drug to treat their seizures when Warner-Lambert knew the medication did not work. In other promotional material, the company promoted gabapentin for the use of bipolar disorder when a study demonstrated that a placebo worked as well or better than the drug.[223] These examples provide support for the notion that off-label promotion may influence prescribers into using drugs that are not effective, and thus prescribing a drug to a patient that does not work.

Drug sales and stock price implications

Although it represented the second largest settlement of its kind at the time, the settlement amount of $430 million amounted to 3.5% of overall worldwide sales for gabapentin from 1998 to 2004.[224] Even taking into account research and development costs, legal fees and other promotional expenses, the profits from illegally promoting the drug seem to have outweighed any legal ramifications.

From mid-1995 through at least 2001, the growth of gabapentin off-label sales was tremendous.[225] Gabapentin sales increases support this statement. From 1998 to 2002, gabapentin moved from number 77 in overall worldwide sales to number 14 in

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[221] *Id.*
[222] *Id.*
[223] *Id.*
[224] *See* MedAdNews, The magazine of pharmaceutical business and marketing, *The Top 500 Prescription Drugs by Worldwide Sales* (May 1998 to 2002).
[225] *Id.*

2002.[226] The average percent growth in overall sales per year over this timeframe was 52%. In 2004, when Warner-Lambert pled guilty and settled allegations of illegal promotion of gabapentin, the percent growth in overall sales for the year was only 0.8% compared to an average of 52% before Warner-Lambert agreed to a settlement based on their illegal promotional practices.

4.1.3 Evista®—Eli Lilly & Co.

Overview

On December 21, 2005, the DOJ announced the third off-label settlement between the federal government and a pharmaceutical company.[227] Eli-Lilly & Company agreed to plead guilty and to pay $ 36 million to settle allegations of illegal promotion of Evista® (raloxifene).[228] Eli-Lilly pled guilty to a criminal count of violating the Food, Drug, and Cosmetic Act by misbranding Evista.[229] In addition to the criminal fine, Lilly agreed to settle civil FDCA liabilities by entering into a consent decree of permanent injunction and paying the United States $24 million in equitable disgorgement.[230] As part of the settlement, Lilly agreed to be permanently enjoined from directly or indirectly promoting Evista for use in preventing or reducing the risk of breast cancer, reducing the

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[226] *See* MedAdNews, The magazine of pharmaceutical business and marketing, *The Top 500 Prescription Drugs by Worldwide Sales*, (May 1998 to 2002); *see also*, Off-Label Promotion at 2(stating that from 1994 to 2002, sales of Neurontin to the Department of Veterans Affairs jumped from $287,000 to $43.2 million.
[227] The Enforcement Story, Office of Criminal Investigations, FY 2006 Report.
[228] *Id.*
[229] *Id.*
[230] *Id.*at 6-9.

risk of cardiovascular disease, or for any other unapproved use in a manner that violates the FDCA.[231]

Clinical

The FDA approved Evista on December 9, 1997 for the prevention of osteoporosis in postmenopausal women.[232] A list of the indications and off-label uses per drug as published in the AHFS from 1997 through 2010 is available upon request. As of May 2010, raloxifene is indicated by the FDA for the following conditions: (1) for the treatment and prevention of osteoporosis in postmenopausal women; (2) for the reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis; (3) for the reduction in risk of invasive breast cancer in postmenopausal women at high risk of invasive breast cancer.[233] During the time frame where Lilly was illegally promoting raloxifene, the only approved indication was treatment and prevention of osteoporosis in postmenopausal women.[234] Raloxifene has since received approval for reduction in the risk of specific types of breast cancer, but there is no evidence that raloxifene decreases the risk of cardiovascular disease.[235] Furthermore, the drug information on raloxifene

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[231] *Id.* at 6-9.
[232] www.fda.gov/drugs
[233] MICROMEDEX® Healthcare Series, Physician's Desk Reference (PDR), Evista® drug profile, at § 1.
[234] Complaint United States v. Eli Lilly Co. No. 05-cv-1884, Dec. 21, 2005 (S.D. Indiana), at ¶ 14.
[235] MICROMEDEX® Healthcare Series, Physician's Desk Reference (PDR), Evista® drug profile, at § 1.

lists multiple types of breast cancer where there is no evidence that raloxifene decreases risks of cancer.[236]

Factual Allegations & Admissions

The allegations stemmed from the marketing department, and more specifically, what Lilly referred to as its "Evista Brand Team," and sales representatives promoting Evista (raloxifene) for the prevention and reduction in the risk of breast cancer and the reduction in the risk of cardiovascular disease.[237] The DOJ press release singled out activities such as creating and distributing to sales representatives an "Evista Best Practices" videotape, in which a sales representative states that "Evista truly is the best drug for the prevention of all these diseases" referring to osteoporosis, breast cancer, and cardiovascular disease.[238]

Lilly asserted that raloxifene (Evista) had multiple benefits besides just as a treatment and prevention of osteoporosis, which is the only indication for other drugs that treat and prevent osteoporosis such as alendronate (Fosamax).[239] Thus, the marketing messages were an attempt to distinguish raloxifene (Evista) from other drugs already available. For example, in *Prevention Magazine* Lilly stated that raloxifene (Evista) "[P]revents osteoporosis… lowers cholesterol… Addresses concerns about breast

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[236] MICROMEDEX® Healthcare Series, Physician's Desk Reference (PDR), Evista® drug profile, at § 1 (list the types here…)
[237] Complaint Lilly ¶ 20.
[238] Press Release, Department of Justice Eli Lilly and Company To Pay U.S. $36 Million Relating To Off-Label Promotion (December 21, 2005), http://www.justice.gov/opa/pr/2005/December/05_civ_685.html; Complaint Lilly at ¶ 20.
[239] Complaint Lilly ¶ 20.

cancer."[240] Lilly received an FDA Notice of Violation based on the advertisement stating that "This advertisement is misleading because it overstates Evista's benefits… this advertisement implies that Evista is indicated for a broader range of uses than supported by the product's FDA approved labeling."[241] In another letter from the FDA, Lilly was informed that a Press Release inappropriately insinuated that raloxifene (Evista) was approved for other uses.[242]

During and after these Notices of Violation from the FDA, Lilly implemented and carried out "Evista's Three Combined Benefits Message" to doctor's.[243]

Evista addresses three significant concerns of your postmenopausal patients: "Evista builds bone. Evista for the prevention of postmenopausal osteoporosis. Evista addresses their concerns about breast cancer. Evista improves the lipid profile."[244] The Complaint also noted an interesting finding by Lilly's Market Research's Tech group where the group calculated which activities resulted in the largest shift in physician prescribing.[245] Advisory Board meetings, which included discussions of unapproved uses, were the most likely to result more raloxifene prescriptions for doctors who attended.[246]

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[240] *Id.* ¶ 22.
[241] *Id.* ¶ 23.
[242] Complaint Lilly ¶ 25; Department of Health and Human Services, FDA Warning Letter transmitted to Micheal P. Bigelow, Attorney Eli Lilly and Company (Dec. 23, 1998), available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/UCM166589.pdf.
[243] Complaint Lilly ¶ 26.
[244] Complaint United States ex rel. Sandra Boucher et al. v. Serono Labs., No. 05-cv-10722 (D. Maryland) at ¶ 26.
[245] *Id.* ¶ 32.
[246] *Id.* ¶ 32.

4.1.4 Serostim®—Serono, Inc.

Overview

On October 17, 2005, Serono, S.A. agreed to pay $704 million in connection with illegal schemes to promote, market, and sell Serostim. Serono Laboratories agreed to pay $ 136.9 million criminal fine, and its affiliate companies a total of $ 567 million to settle civil liabilities.[247] Under the civil settlement, Serono paid $305 million plus interest to the U.S. for losses suffered by the federal portion of the Medicaid program, Veteran's Administration, Department of Defense, and Federal Employees Health Benefits program.[248] Under separate settlement agreements with the states, Serono paid $262 million plus interest to state Medicaid programs. Serono also agreed to enter into a Corporate Integrity Agreement.[249] The whistleblowers shared $51.8 million as part of the settlement.[250]

Serono Labs also agreed to plead guilty to charges that it conspired with medical device manufacturer RJL Sciences to market bioelectrical impedance analysis (BIA) computer software packages for use in calculating body cell mass and diagnosing AIDs wasting.[251]

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[247] Press Release, Dep't of Justice, Serono to Pay $704 Million For The Illegal Marketing of AIDS Drug (Oct. 17, 2005), available at http://www.usdoj.gov/opa/pr/2005/October/05_civ_545.html [hereinafter Serono Press Release].
[248] *Id.* at 1–2.
[249] *Id.* at 2.
[250] *Id*. at 2.
[251] *Id.* (the drug had not been approved for these uses as of the date of the settlement).

The settlement included reimbursement of the state Medicaid agencies for "all monies paid based on Serono's illegal activity" during the time frame of the investigation.[252] The time frame noted in the Press Release was 1996 through 2004.[253] The Press Release stated that the settlement would repay, with interest, the losses to federal and state Medicaid programs incurred by Serono's conduct, "and would-be wrongdoers are on notice that we will not tolerate attempts to profit at the expense of the ill and needy in our society."[254]

As a result of the criminal conviction, Serono Labs was excluded from all federal health care programs for at least five years.[255] As part of the civil settlement, Serono's U.S. subsidiary, Serono Holding and all U.S. affiliates agreed to a five year Corporate Integrity Agreement.[256] Serostim continued to be sold by Schering-Plough to all federal health care programs after the settlement.

Clinical

The FDA approved Somatropin (Serostim) on August 23, 1996 for treatment of AIDS wasting in HIV-infected patients.[257] Somatropin (Serostim) is a mammalian cell derived human growth hormone (r-hGH) which is identical to endogenous human growth hormone. The FDA granted accelerated approval for Serostim. At the time, AIDS wasting was one of the leading causes of death among AIDS patients. AHFS did not

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[252] *Id.*
[253] *Id.*
[254] *Id.*
[255] *Id.*
[256] *Id.*
[257] Orange Book, www.fda.gov (Aug. 23, 1996 for the 6 and 5 mg vials and July 25, 1997 for the 4 mg vials).

publish the uses for Serostim so information was collected using Micromedix by Thomson Reuters and the FDA's website.

Factual Allegations & Admissions

Former employees brought a lawsuit against Serono, Inc. in 2000 in Massachusetts, and four other employees filed similar suits in Maryland and Connecticut.[258] The Massachusetts Complaint request damages and civil penalties on behalf of the United States of American and eleven states arising from false statements and claims made by Serono in violation of the Federal False Claims Act.[259]

The Complaint alleges that Serono promoted Serostim for lypodystrophy. Serono provided sales representatives with unsolicited articles about using Serostim for lypodystrophy that were not peer-reviewed and not published in scientific or medical journals or reference publications, as required by law.[260]

The Complaint alleged that Serono provided its sales representatives with Bioelectrical Impedance Analysis (BIA) machines in order to determine a patient's lean body mass, which is a prerequisite to a diagnosis of AIDS wasting.[261] Serono offered patients gift certificates, phone cards, and bus tokens in exchange for taking a BIA test.[262] The Complaint further alleged that Serono instructed its sales staff to perform BIA testing using BIA machines that Serono owned, and provided to its sales representatives.[263]

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[258] Amended Complaint United States et al, ex rel. Frank Garcia & Christine Discolli v. Serono, Inc., No. 03-cv-11892, Oct. 10, 2003 (D. Mass.), ¶ 1.
[259] *Id.* ¶ 1.
[260] *Id.* ¶ 32.
[261] *Id.* ¶ 25.
[262] *Id.*
[263] *Id.*

Serono's BIA machines were "deliberately programmed to generate a deceptive report," which included language suggesting that the treating physician created the report.[264] The reports were used for billing insurance companies. Serono sales representatives assisted doctors with billing the results to insurance companies.[265]

The complaint also alleged that in 1999 and 2000, sales representatives provided checks and free BIA machines to physicians or physician's assistants in exchange for writing a Serostim prescription.[266] The Complaint alleges that this activity violates the Anti-Kickback Statute.[267] The Complaint also alleges that sales representatives offered to or paid the cost of transportation for patients to see physicians who wrote prescriptions for Serostim.[268] The vast majority of the Serostim patient population relied upon Medicaid.

RJL and its president, Rudolph J. Liedtke, plead guilty to their roles in the conspiracy in April of 2005.[269] Serono Labs plead guilty to offering physicians an all expense paid trip to France in return for the doctors writing 30 new prescriptions of Serostim.[270] Serostim cost $21,000 per course of treatment at the time, for a total value of $630,000 per doctor.[271] Additionally, Serono provided unsolicited articles to physicians about the benefits of Serostim for the treatment of lypodystrophy.[272] These

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[264] *Id.* ¶ 28.
[265] *Id.* ¶¶ 28,29.
[266] *Id.* ¶ 30.
[267] *Id.* ¶30.
[268] *Id.* ¶ 31.
[269] *Id*.
[270] *Id*.
[271] *Id*.
[272] Complaint ¶ 32.

articles were neither peer-reviewed nor published in scientific or medical journals or reference publications.[273]

4.1.5 Temodar® & Intron A—Schering-Plough Corp. I

Overview

On August 29, 2006 the Department of Justice announced that Schering-Plough Corp., together with subsidiary, Schering Sales Corp. agreed to pay a total of $435 million to resolve criminal charges and civil liabilities in connection with illegal sale and marketing programs for Temodar and Intron A (the resolution also pertains to Medicaid Best Price fraud involving Claritin RediTabs and K-Dur).[274] Schering Sales Corp. will pay a $180 million criminal fine, and together with Schering-Plough Corp., another $255 million to settle civil liabilities.[275] Schering Sales Corp. pled guilty to one count criminal conspiracy to make false statements to both the FDA regarding its improper drug promotional activity and to HCFA regarding its best price for certain drugs.[276] As a result of its criminal convictions, Schering Sales "will be excluded permanently from participation in all federal health care programs."[277] As discussed above, the "permanent exclusion" resulted in Schering simply shutting down Schering Sales Corporation and moving operations and personnel to another entity under Schering Plough Corporation.

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[273] *Id.*
[274] Press Release, U.S. Dept. of Justice, Michael J. Sullivan U.S. Attorney, D.Mass., Schering to Pay $435 Million for the Improper Marketing of Drugs and Medicaid Fraud; Aug. 29, 2006.
[275] Press Release Temodar, at 1.
[276] Press Release Temodar, at 2.
[277] Press Release Temodar, at 3.

> SCHERING PLOUGH CORPORATION also agreed to settle its civil False Claims Act liabilities and liabilities under the Food Drug and Cosmetic Act for a total of $255,025,000. Specifically, SCHERING will pay $159,502,000, plus interest, to the United States in civil damages for losses suffered by the Medicare program, the federal portion of the Medicaid program, the Veteran's Administration, the Department of Defense and the Federal Employees Health Benefits program as a result of SCHERING's improper drug promotion and marketing misconduct, and Medicaid rebate fraud. SCHERING will also pay a total of $91,602,000, plus interest, to settle its civil liabilities to the fifty states and the District of Columbia for losses the state Medicaid programs suffered. In addition, SCHERING will refund $3,921,090 to the Public Health Service (PHS) programs that also were entitled to a lower price on certain drugs.[278]

The criminal conspiracy included Schering Sales pleading guilty to charges that it conspired with others to make false statements to the FDA in response to the FDA's inquiry regarding illegal promotional activities by the Company's sales representatives at a national medical conference for oncologists.[279] The civil settlement resolved allegations that Schering:

> (1) SCHERING misreported its best price to HCFA on Claritin RediTabs to evade Medicaid rebate liability, (2) SCHERING misreported its best price on private-labeled K-Dur to HCFA to evade Medicaid rebate liability, (3) SCHERING overcharged the PHS entities because of its misreporting of best price to HCFA, (4) SCHERING induced physicians to start patients on Intron A for Hepatitis C by paying them remuneration through three marketing programs, (5) SCHERING induced physicians to use Temodar for certain patients with brain tumors and brain metastases and to use Intron A for certain patients with superficial bladder cancer through improper preceptorships, sham advisory boards, lavish entertainment, and improper placement of clinical trials; and (6) SCHERING knowingly promoted off label uses of Temodar for certain brain tumors and brain metastases and

[278] *Id.*
[279] *Id.* at 3.

> Intron A for superficial bladder cancer despite not having FDA approval.[280]

Schering had a CIA already in place due to previous fraudulent conduct, and thus, part of the settlement included amendments to the existing CIA.[281]

Clinical

The FDA approved the 20 mg, 100 mg, and 250 mg temozolomide (Temodar) capsules on August 11, 1999[282] for the treatment of refractory anaplastic astrocytoma (a type of brain tumor unresponsive to first line treatment), recurrent glioblastoma multiforme (another type of brain tumor unresponsive to first line treatment), and metastatic malignant melanoma (skin cancer that has metastasized to the brain). Temodar received a priority review and Orphan drug status. The FDA approved interferon alpha-2b (Intron A) on June 4, 1986. Intron A is indicated for the treatment of various conditions, including but not limited to, chronic hepatitis B, AIDs-related Kaposi's sarcoma, hairy cell leukemia, malignant melanoma and follicular lymphoma. A list of the indications and off-label uses per drug as published in the AHFS from 1997 through 2010 is available upon request.

Factual Allegations & Admissions

From about early 1998 through about August 2001, "the exact dates unknown," the Complaint alleges that Schering "knowingly and willfully combine, conspire and agree to knowingly and willfully make materially false, fictitious and fraudulent

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[280] *Id*. at 3.
[281] *Id*. at 3.
[282] www.fda.gov/drugs (the 140 mg and 180 mg capsules were approved October 19, 2006).

statements and representations…" [283] The Complaint includes allegations of best price violations regarding the drug Claritin Reditabs.[284] The Complaint also includes allegations of off label promotion regarding the drugs Temodar and Intron A.[285] The Complaint alleges that the violations amounted to the retention of $4,392,000 from rebates owed to state Medicaid programs for Claritin Reditabs, and $124,179,000 in before-tax profits for Temodar and Intron A which would otherwise have not been obtained by Schering Sales.

The Complaint identified early 1998 to about August 2001, "the exact dates unknown" as the timeframe when the conspiracy occurred. On or about June 29, 2001, Schering Sales received a copy of an untitled letter dated June 28, 2001 from DDMAC concerning a May 2001 commercial exhibit hall booth that Schering maintained and staffed with representatives of OBBU sales force at the 37th American Society of Clinical Oncology ("ASCO") Annual Meeting.[286] The letter notified Schering that it had provided "false or misleading efficacy information about Temodar to visitors at the commercial exhibit hall booth" at the ASCO meeting and that "Schering also promoted Temodar for the unapproved use in first line therapy of anaplastic astrocytoma" when it was only approved as a second line treatment option.[287] The letter requested Schering

[283] Complaint United States v. Schering Sales Corp. (a subsidiary of Schering-Plough Corp, No. 06-cr-10250 (D. Mass.), ¶ 18.
[284] *Id* ¶ 20a.
[285] *Id*. ¶ 20b.
[286] Complaint at 12.
[287] Complaint at 13.

submit a written response to the FDA on or before July 13, 2001, and provide a date where such "violative materials were discontinued."[288]

In response to the FDA letter, Schering sent a response on July 12, 2001 that the Complaint alleged included "false assurances designed to lull the FDA into believing that effective remedial action had been taken in order to avoid further FDA scrutiny of Schering promotional activity."[289] The Complaint alleges that the result of the "false statements to the FDA to avoid scrutiny of the ongoing off-label promotional activities directed by home office, Schering Sales and its co-conspirators caused Schering to obtain, between July 2001 and December 2003 about $124,790,000 in before-tax profit to which it was not entitled."[290]

4.1.6 Actimmune®—InterMune, Inc.

Overview

On October 26, 2006, the Department of Justice announced that InterMune Inc. agreed to pay $36.9 million to resolve criminal charges and civil liabilities for promotional and marketing of Actimmune.[291] The federal portion of the Medicaid program, Medicare program, Veteran's Administration, Department of Defense, and the Federal Employees Health Benefits program received $30.2 million.[292] As part of the

[288] Complaint at 13.
[289] Complaint at 14.
[290] Compaint at 15.
[291] Press Release, Biopharmaceutical Firm Intermune to Pay U.S. Over $36 Million for Illegal Promotion and Marketing of Drug Actimmune, Department of Justice, Oct. 26, 2006.
[292] *Id.*

civil settlement agreement with the states, InterMune paid nearly $6.7 million to state Medicaid programs.[293] The criminal investigation was deferred for two years upon entry of a deferred prosecution agreement (DPA) with the United States.[294] InterMune also agreed to enter a five year Corporate Integrity Agreement.[295]

For at least 5 months, the majority of Actimmune prescriptions were for an off label use. According to the Press Release, the "vast majority" of Actimmune prescriptions were for idiopathic pulmonary fibrosis (IPF) during the period of August 2002 through January 2003.[296]

Clinical

The FDA approved Actimmune on February 25, 1999 to reduce the frequency and severity of serious infections in adults and children 1 year of age or older with chronic granulomatous disease and to delay the time to disease progression in adults and children with severe, malignant osteopetrosis. A list of the indications and off-label uses per drug as published in the AHFS from 1997 through 2010 is available upon request.

On March 9, 2007, the FDA issued an alert related to the efficacy of Actimmune for IPF:

> FDA ALERT [3/9/2007]: FDA is issuing this alert to advise you of the early termination of the INSPIRE clinical study of Actimmune for idiopathic pulmonary fibrosis (IPF). The study was stopped because an interim analysis showed that patients with IPF who received Actimmune did not benefit. The trial compared survival in patients getting Actimmune or an inactive injection (placebo).

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[293] *Id.*
[294] *Id.*
[295] *Id.* at 2.
[296] *Id.* at 2.

> An analysis showed that 14.5% of patients treated with Actimmune died as compared to 12.7% of patients treated with placebo. Actimmune is not approved by the FDA to treat IPF.

Factual Allegations & Admissions

The criminal Complaint alleged that off-label promotion of Actimmune resulted in it being misbranded. The Complaint states that from at least August 2002 through at least January 2003, Intermune promoted Actimmune for treatment of idiopathic pulmonary fibrosis (IPF), an off-label use. The Civil Settlement Agreement states that the government contends the off-label promotion occurred between January 1, 2001 through June 30, 2003.

The Civil Settlement Agreement contends that despite a Phase III clinical trial of Actimmune for the treatment of IPF that failed to reach statistically significant benefits on its primary endpoint or any secondary endpoints, certain InterMune employees encouraged the sales force to tell physicians that the trial did in fact demonstrate a survival benefit. After receiving the study results, executives from InterMune told employees to conduct additional analyses of the survival data.[297] The data was separated into subgroups, which enabled a showing of a survival trend for patients whose IPF was described as "mild to moderate."[298] The FDA rejected the results as inconclusive and required Actimmune to do another trial, which ultimately failed to show improved survival in patients with "mild to moderate" IPF.[299] Nevertheless, the trial results found to be inconclusive by the FDA and not statistically significant were conveyed to

[297] United States of America v. Scott Harkonen, No. 08-cr-0164, Mar. 18, 2008 (N.D. CA.) ¶ 16.
[298] *Id.* ¶ 16.
[299] *Id.* ¶¶ 17-19.

prescribers and the public by InterMune's sales force as evidence that Actimmune improved survival in patients with IPF.[300]

Sales of Actimmune totaled $11,201,000 in 2000; $36,320,000 in 2001; $105,802,000 in 2002; $141,402,000 in 2003.[301] The vast majority of Actimmune sales were for treating IPF, an off-label use.[302]

4.1.7 Genotropin®—Pfizer Inc. II (Pharmacia & Upjohn Co.)

Overview

In April of 2007, Pharmacia & Upjohn Co. LLC, a subsidiary of Pfizer, paid $34,680,000 million and entered a deferred prosecution agreement for its illegal promotion of Genotropin, and settled off label allegations.[303] Pharmacia & Upjohn Co. LLC paid $15 million to settle allegations that it promoted the drug for anti-aging, cosmetic use, and athletic performance enhancing purposes.[304] A second Pfizer subsidiary, Pharmacia & UpJohn Co., Inc., pled guilty to violations of the Anti-Kickback Act and paid a criminal fine of $19.68 million.

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[300] *Id.* ¶ 23.
[301] United States of America v. Scott Harkonen, No. 08-cr-0164, Mar. 18, 2008 (N.D. CA.) ¶ 7.
[302] *Id.* ¶ 7.
[303] Health Care Fraud, 57 United States Attorneys' Bulletin 1, 8–9 (Jan. 2009).
[304] *Id.*

According to the Corporate Crime Reporter, one U.S. Attorney said that Pfizer acted responsibly for voluntarily and fully self-disclosing the off-label promotion of Genotropin.[305]

Clinical

The FDA approved Genotropin in August 1995 for treatment of pediatric patients who have growth failure due to an inadequate secretion of endogenous growth hormone ("GH"); treatment of pediatric patients who have growth failure due to Prader-Willi syndrome, a rare genetic disorder that causes short stature and other disabilities (June 2000); and treatment of growth failure in children born small for gestational age ("SGA") who fail to manifest catch-up growth by age two (this is a specific diagnosis that refers to infants who have a birth weight or length that is more than two standard deviations below mean normal values) (July 2001); and adults with growth hormone deficiency (November 1997). The AHFS never published information on the indications and uses for Genotropin. As a result, indications were collected from Micromedix by Thomson Reuter and the FDA's website.

Factual Allegations & Admissions

Dr. Peter Rost initiated the lawsuit as a whistleblower.[306] Pharmacia has employed Dr. Rost as Vice President in charge of the Endocrine Care Unit since June 2001.[307] The Complaint requests damages and civil penalties on behalf of the United

[305] Pfizer Unit Pleads Guilty, Prosecutors Praise the Corporate Criminal, Not The Whistleblower, 21 Corporate Crime Reporter 15 (Apr. 3, 2007).
[306] Complaint, United States of America ex rel. Dr. Peter Rost v. Pfizer Inc. and Pharmacia Corp., No. 03-cv-11084, June 5, 2003 (D. Mass.).
[307] *Id.* ¶ 9.

States and states arising from off-label promotion of Genotropin.[308] The timeframe alleged is about the beginning of 1997 through at least June 2003.[309] The off-label promotion, included, but was not limited to, promoting the drug for anti-aging in adults, and short stature in children unrelated to growth hormone deficiency.[310]

According to the Complaint, Mr. Rost, upon his hiring in June 2001, discovered the following off-label promotional activities: superiors requesting sales representatives to market and promote Genotropin for off-label uses; a large study program to financially reward physicians for prescribing Genotropin on and off-label and to promote off-label uses; encouraging the sales force to promote the drug to physicians working in the area of anti-aging; promoting the drug for pediatrics and for the treatment of childrenshort for their age not due to GH deficiency; promoting to children with Turner's syndrome; providing direct payments to physicians for prescribing Genotropin; and paying lucrative consulting fees to promote off-label uses.[311]

According to the Complaint, the off-label promotion began on or about 1997.[312] From 1998 to 2002, annual sales revenue for Gentropin more than tripled, reaching $150 million in 2002.[313]

The 2003 Complaint state that about 60% of all adult sales and 25% of pediatric sales of Genotropin were off-label.[314] This translates into $50 million in off-label sales

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[308] *Id.*
[309] *Id.* ¶ 2.
[310] *Id.* ¶ 2.
[311] *Id.* ¶ 59.
[312] *Id.* ¶ 60.
[313] Complaint ¶2.
[314] Pfizer Complaint ¶ 3.

for Genotropin in 2002.[315] The Complaint states that total off-label sales of Gentropin since 1995 amounts to hundreds of millions of dollars.[316]

The 2003 Complaint states that fewer than 50,000 adults have growth hormone deficiency, and only about 6,000 new cases are diagnosed each year. Genotropin sales revenues rose from negligible shortly after introduction in 1995, to $54 million in 1999 to $69 million in 2000, $115 million in 2001, and about $150 million in 2002.

4.1.8 Oxycontin®—Purdue Frederick Co.

Overview

In May 2007, Purdue Fredrick Company, Inc. and certain company executives, plead guilty to charges of misbranding the drug Oxycontin (extended-release oxycodone) with the intent to defraud and mislead.[317] The settlement totaled $634,515,475 and included $160 million paid to the federal and state government agencies to resolve false claims made to Medicaid and other government programs; $276.1 million forfeited to the United States; $130 million for private civil claims (monies remaining after 36 months will be paid to the United States); $5.3 million to Virginia's Medicaid Fraud Control Unit to fund future health care fraud investigations; $20 million paid to the Virginia

[315] *Id.* ¶ 3.
[316] *Id.* ¶ 3.
[317] Press Release U.S. Attorney's Office Western District Of Virginia, The Purdue Frederick Company, Inc. and Top Executives Plead Guilty to Misbranding Oxycontin; will Pay over $600 Million, (May 10, 2007), http://www.usdoj.gov/usao/vaw/press_releases/purdue_frederick_10may2007.html [hereinafter Press Release Oxycontin].

Prescription Monitoring Program; $500,000 statutory criminal fine (the maximum).[318] The guilty pleas stemmed from fraudulent marketing schemes that promoted oxycodone-CR (Oxycontin) as less addictive, less subject to abuse, and less likely to cause withdrawal symptoms than other pain medications when there was no medical research to support these claims, and without FDA approval of these claims.[319]

Clinical

The FDA approved Oxycontin on December 21, 1995 for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time; uses include the treatment of cancer pain and nonmalignant pain, such as back pain, osteoarthritis-related pain, and pain during rehabilitation following total knee arthroplasty.[320] A list of the indications and off-label uses per drug as published in the AHFS from 1997 through 2010 is available upon request.

Studies comparing oxycodone-CR and immediate release oxycodone have shown comparable efficacy and safety for use with chronic back and cancer-related pains.[321]

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[318] *Id*.
[319] *Id*.
[320] MICROMEDEX® Healthcare Series, Physician's Desk Reference (PDR), Oxycontin® drug profile.
[321] ME Hale et al. *Efficacy and safety of controlled-release versus immediate-release oxycodone: randomized, double-blind evaluation in chronic back pain*. 15 Clin J Pain, 179–183 (1991); R Kaplan et al. Comparison of controlled-release and immediate-release oxycodone in cancer pain, 16 J Clin Oncol, 3230–3237 (1998); JE Staumbaugh et al. *Double-blind, randomized comparison of the analgesic and pharmacokinetic profiles of controlled-and immediate-release oral oxycodone in cancer pain patients*, 41 J Clin Pharmacol, 500–506 (2001); R Chou et al. *Comparative efficacy and safety of long-acting oral opioids for chronic non-cancer pain*, 26(5) J Pain Symptom Manage, 1026-1048 (2003).

Studies comparing oxycodone-CR (OxyContin) with controlled-release morphine (MS Contin) for cancer-related pain have also found comparable efficacy and safety.[322]

Factual Allegations & Admissions

The promotional schemes employed by Purdue led prescribers into believing that the drug was safer and less addictive than other pain medications. In particular, Purdue engaged in a marketing strategy that encouraged its sales representatives to assert that oxycodone-ER (Oxycontin) was more potent than MS Contin (morphine sulphate), and that as a result, it was much less expensive. Morphine sulfate (MS Contin) was also marketed by Purdue, but the patent on MS Contin expired in 1996 so generic companies were allowed to make the drug, which resulted in a decline in the price of morphine sulfate (MS Contin).

Due to the expected expiration of the patent on morphine sulfate (MS Contin), Purdue began marketing oxycodone-CR (Oxycontin) in 1995.[323] Purdue's marketing strategy centered on convincing physicians to switch from morphine sulfate (MS Contin) to oxycodone-CR (Oxycontin),[324] once the patent expiration was near and imminent. Purdue went farther; however, in asserting that it took only one milligram of oxycodone-CR (Oxycontin) to achieve the same pain relief as two milligrams of morphine sulfate (MS Contin). Thus, Purdue trained sales representatives to state that as a result, oxycodone-CR (Oxycontin) was actually cheaper than morphine sulfate (MS Contin)

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[322] Bruera E et al. *Randomized, double-blind, cross-over trial comparing safety and efficacy of oral controlled-release oxycodone with controlled-release morphine in patients with cancer pain*, 16 J Clin Oncol, 3222–3229 (1998).
[323] Third Amended Complaint, United States ex rel. Radcliffe v. Purdue Pharma , No. 05-cv-00089, June 5, 2007 (W.D. Va.).
[324] Complaint Purdue at ¶ 10.

when leaders of the marketing department were well aware that this was false.[325] For instance, in one document attached to the Complaint, it is clear that Purdue provided prices of the two drugs and fraudulently claimed that a 30-day supply of morphine sulfate (MS Contin) was more expensive than a 30-day supply of oxycodone-CR (Oxycontin).[326]

Purdue based its 2:1 ratio claim on a single dose study. This single dose study examined the drugs for treatment of acute, short-term pain.[327] The FDA has not approved either drug for short-term use.[328] In fact, Purdue knew that when using a ratio that included using the drugs for chronic pain as indicated, the ratio of morphine sulfate (MS Contin) was greater, not less, than that of oxycodone-CR (Oxycontin).[329] The Complaint notes that some physicians the whistleblower talked to while a sales representative at Purdue dismissed the claims that he was trying to make.[330] He noted that these physicians had advanced knowledge of pain management.[331]

In response, the Complaint alleges that in 1997, Purdue changed its focus to physicians and others less aware of the pharmacokinetics of pain medications, and who had less experience in long–term pain management.[332] Purdue included in this targeted group surgeons, internists, family practice physicians, and other primary care

[325] Complaint Purdue at ¶ 11.
[326] See Complaint Purdue at ¶ 11, exh. 1.
[327] Complaint Purdue ¶ 12.
[328] *Id.*
[329] *Id.*
[330] Complaint Purdue ¶¶ 17–19.
[331] *Id.*
[332] Complaint Purdue ¶ 20–21.

physicians.[333] By 2003, nearly one-half of all physicians prescribing oxycodone-CR (OxyContin) were primary care physicians.[334]

The marketing department also provided Guides for sales representatives that cited to studies that did not exist.[335] The misleading tactics resulted in people dying from using the medication, and an even greater number of people becoming addicted to the drug.[336] Daniel Levinson, Inspector General for the U.S. Department of Health and Human Services, stated that the illegal sales and marketing practices of oxycodone-CR (Oxycontin) concealed information regarding potency and abuse potential "for corporate profit."[337]

This case is especially disturbing because the executives and management of Purdue knew the addictive nature of the drug, and its relative potency compared to other pain medications, but created marketing and promotional materials that directly contradicted their own data.[338]

Sales of oxycodone-CR (Oxycontin) grew from $ 48 million in 1996 to almost $ 1.1 billion in 2000.[339] By 2001 sales reached almost $1.5 billion, with 6.8 million prescriptions that year.[340]

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[333] Complaint Purdue ¶ 21.
[334] Prescription Drugs: OxyContin Abuse and Diversion and Efforts to Address the Problem. Washington, DC: General Accounting Office; December 2003. Publication GAO-04-110; Zee Van, *The Promotion and Marketing of OxyContin: Commercial Triumph, Public Health Tragedy* 99 Am J Public Health 221–227 (2009).
[335] Complaint Purdue ¶ 22.
[336] Press Release Oxycontin at 4.
[337] *Id*. at 2.
[338] *Id*. at 2, 3.
[339] Zee Van, *The Promotion and Marketing of OxyContin: Commercial Triumph, Public Health Tragedy* 99 Am J Public Health, 221–227 (2009).

4.1.9 Abilify®—Bristol-Myers Squibb (Apothecon Inc.) and separately, Ostuka

Overview

On September 28, 2007, the Department of Justice announced that Bristol-Myers Squibb Company and its wholly owned subsidiary, Apothecon, Inc., agreed to pay over $515 million to resolve a broad array of civil allegations involving multiple drugs that included off-label promotion of Abilify.[341] The federal recovery is over $328 million, of which over $25 million constitutes disgorgement of profits under the FDCA resulting from BMS's illegal promotion.[342] BMS also paid over $187 million to the Medicaid participating states, and $124,000 to certain Public Health Service entities.[343] The whistleblowers received a total of approximately $50 million of the settlement.[344]

The settlement included multiple different allegations against BMS for multiple drugs sold by BMS (over 50 drugs). First, the Government alleged that, from approximately 2000 through mid-2003, BMS paid kickbacks to physicians and other health care providers to induce them to purchase BMS drugs.[345] The Government also alleged that, from 1994 through 2001, Apothecon paid kickbacks in the form of stocking

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[340] Complaint Purdue ¶ 28.
[341] Press Release, Bristol-Myers Squibb to Pay More Than $515 Million to Resolve Allegations of Illegal Drug Marketing and Pricing, Department of Justice (Sept. 28, 2007).
[342] *Id.*
[343] *Id.*
[344] *Id.*
[345] *Id.*

allowances, price protection payments, rebates, market share payments, and free goods in order to induce its retail pharmacy and wholesaler customers to purchase its products.[346]

Second, the Government alleged that, from 2002 through the end of 2005, BMS knowingly promoted off-label uses of Abilify (pediatric use and to treat dementia-related psychosis).[347] The FDA has mandated that the package for Abilify carry a "black box" warning concerning its use in the treatment of dementia-related psychosis.[348] According to the Press Release, BMS directed its sales force to call on child psychiatrists and other pediatric specialists, and urge these physicians and other providers to prescribe Abilify for pediatric patients.[349] BMS also created a specialized long term care sales force that called almost exclusively on nursing homes, where dementia-related psychosis (off-label use) is far more prevalent than schizophrenia or bipolar disorder (FDA indications for Abilify).[350]

Third, the Government alleged that both BMS and Apothecon set and maintained fraudulent and inflated prices for a wide assortment of oncology and generic drug products, knowing that the federal health care programs established reimbursement rates based on those prices.[351] Finally, the Government alleged that BMS knowingly misreported its best price for the anti-depression drug, Serzone.[352] BMS did not include

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[346] *Id.*
[347] *Id.*
[348] *Id.*
[349] *Id.*
[350] *Id.*
[351] *Id.*
[352] *Id.*

the price at which it sold "private-label" Serzone to Kaiser, a large commercial purchaser.[353]

On March 27, 2008, the Department of Justice announced that Otsuka American Pharmaceutical Inc., the American subsidiary of Japanese pharmaceutical manufacturer Otsuka Pharmaceutical Co., Ltd., agreed to pay over $4 million to resolve allegations of off-label promotion of Abilify.[354] The federal recovery was approximately $2.3 million, and the state Medicaid portion[355] approximately $1.7 million.[356] The whistleblower received approximately $348,000 as his share of the federal settlement amount.[357]

Otsuka developed Abilify in Japan and then entered into a contractual agreement with BMS to co-promote sales of the drug in the United States.[358] After entering the agreement, Otsuka sales representatives worked on sales teams led primarily by BMS sales managers.[359] The off-label promotion occurred from 2002 through the end of 2005, as noted above.[360] The Ostuka settlement comprised Ostuka's role in the BMS led promotion of Abilify for pediatric uses and dementia-related psychosis.[361]

The Press Release notes the recent FDA approval of Abilify for treatment of schizophrenia in adolescents aged 13 to 17 years and for treatment of acute manic or

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[353] *Id.*
[354] Press Release, Otsuka to Pay More than $4 Million to Resolve off-label Marketing Allegations Involving Abilify, Department of Justice (Mar. 27, 2008).
[355] Not all states participated.
[356] Press Release, Otsuka to Pay More than $4 Million to Resolve off-label Marketing Allegations Involving Abilify, Department of Justice (Mar. 27, 2008).
[357] I*d.*
[358] *Id*.
[359] *Id*.
[360] *Id*.
[361] *Id*.

mixed episodes associated with Bipolar I Disorder in pediatric patients aged 10 to 17 years.[362]

Clinical

The FDA approved Abilify on August 28, 2003 for the management of schizophrenia, and for the treatment of acute manic and mixed episodes associated with bipolar I disorder in 2006. A list of the indications and off-label uses per drug as published in the AHFS from 1997 through 2010 is available upon request.

Factual Allegations & Admissions

The cases remain sealed in the District of Massachusetts under *United States ex rel. Piacentile v. Bristol-Myers Squibb Co. and Otsuka Pharmaceutical Co., Ltd*., Civil Action No. 05-10196-MLW (D. Mass.). Thus, all information about the factual allegations originates from the DOJ Press Release.

4.1.10 Loprox®—Medicis Pharm. Corp.

Overview

On May 8, 2007 the Department of Justice announced that Medicis agreed to pay the United States $9.8 million to settle allegations that the company violated the False Claims Act for promoting the use of Loprox for use in children under the age of 10 (an off label use).[363] The settlement involves claims made to Medicaid for Loprox.[364] The lawsuit was filed by whistleblowers who alleged that from approximately November

[362] *Id*.
[363] Press Release, Medicis Pharmaceutical To Pay U.S. $9.8 Million to Resolve False Claims Allegations, Department of Justice (May 8, 2007).
[364] *Id.*

2001 through April 2004, Medicis sale representatives promoted Loprox for off label uses.[365] The whistleblowers received in excess of $1,078,000 as their statutory portion of the settlement.

Clinical

The FDA approved Loprox on December 30, 1988 for the treatment of the following skin infections in humans over the age of 10: tinea pedis (athlete's foot), tinea cruris (jock itch), and tinea corporis (ringworm) caused by Trichophyton mentagrophytes, T. rubrum, Epidermophyton floccosum, or Microsporum canis; cutaneous candidiasis (yeast infection that can be found in the groin, toes, finger webs, breasts, umbilical region and skin folds) caused by Candida albicans; and tinea versicolor (a fungus rash that can be found on the upper chest, back shoulders, arms and face) caused by Malassezia furfur (Pityrosporum orbiculare. A list of the indications and off-label uses per drug as published in the AHFS from 1997 through 2010 is available upon request.

Factual Allegations & Admissions

The lawsuit was originally filed by former employees of Medicis Pharmaceuticals, Debbie Mulqueen, Lisa Altazan, Cynthia Hamilton, and Julie Laib.[366] The allegations stemmed from off-label marketing practices that induced false claims to be made to Medicaid.[367] The Complaint alleges that Medicis, after acquiring Ascent in

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[365] *Id.*
[366] Complaint United States of America ex. rel. Debbie Mulqueen, Lisa Altazan, Cynthia Hamilton, Jule Laib v. Medicis Pharmaceutical Corp., No. 04-cv-2389, August 20, 2004 (D. Kansas).
[367] *Id.*

2001[368], aggressively marketed Loprox and Loprox TS to pediatricians as a drug to treat children under the age of 10 with various skin conditions.[369] The practice continued through 2004, and included specific conditions such as diaper dermatitis in babies and toddlers.[370]

In November 2001, a memo was sent to all sales representatives of Medicis's Pediatric Division "instructing them on how to market Loprox for diaper dermatitis in infants and respond to objections from physicians, nurses and pharmacists about using Loprox for off-label uses."[371] The memo highlighted the fact that the cost of Loprox was covered by "managed care plans" and that "pediatric patients have the best prescription coverage (plans/Medicaid)."[372] The Complaint also includes allegations that the Senior Product Manager of Loprox TS stated in a sales training meeting that "pediatricians are high Medicaid- take advantage of this."[373] In 2002, Medicaid provided coverage to 25 million children- more than one in four children in the United States.[374]

In December 2001, the sales representatives were provided with a "Pediatric competitive cheat sheet", and instructed the sales force that Loprox was superior to other topical antifungal products for diaper dermatitis.[375] In 2002, sales representatives were instructed to market Loprox TS as an improved product for diaper dermatitis and

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[368] In November 2001, Medicis merged with Ascent Pediatrics, Inc., which marketed pediatric drugs to pediatricians. Id. ¶12.
[369] *Id*. ¶¶ 28, 81.
[370] *Id*. ¶ 28.
[371] *Id*. ¶ 41.
[372] *Id*. ¶ 42.
[373] *Id*. ¶45.
[374] *Id*. ¶46.
[375] *Id*. ¶50.

cadidiasis.[376] Medicis trained its sales force that cutaneous candidiasis was diaper dermatitis and/or yeast that caused diaper dermatitis.[377] Over the course of three years, Medicis provided sales representatives with talking points, instruction, and marketing brochures in an effort to push prescriptions of Loprox and Loprox TS for pediatric uses to pediatricians.[378] Medicis were also provided with a marketing brochure with off-label marketing techniques where sales representatives were instructed not to leave the brochure with physicians.[379]

The Complaint alleges that Medicis trained sales representatives in "methods of defusing and deflecting" questions from clinicians about the safety and efficacy of Loprox on infants.[380] From 2001 through 2003, sales representatives were told that there was a "Japanese study" on Loprox and infants that just needed to be translated to English.[381] In fact, Medicis never produced such a study.[382]

The Complaint states that for the quarter ending August 2003, there were 28,640 prescriptions for Loprox TS written by pediatricians that Medicis targeted with off-label

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[376] *Id*. ¶¶55, 58.
[377] *Id*. ¶ 59.
[378] *Id*. ¶¶ 51, 55, 58, 61, 63, 64, 67-70.
[379] *Id*. ¶69. Medicis instructed sales representatives to use the brochure as a visual aid in urging pediatricians to write prescriptions for Loprox TS.
[380] *Id*. ¶¶ 71-73. One memo given to sales representatives included the statement: "Loprox is safe- indicated in pediatric patients, contains no propylene glycol; and has a low incidence of adverse reactions." *Id*. ¶ 73.
[381] *Id*. ¶ 77.
[382] *Id*. ¶¶ 77, 78.

marketing techniques and materials.[383] These numbers exclude prescriptions written for Loprox cream.[384]

4.1.11 Trisenox®—Cell Therapeutics Inc.

Overview

On April 17, 2007, the Department of Justice announced that Cell Therapeutics Inc. (CTI) agreed to pay $10.5 million to resolve allegations of illegal marketing (off-label promotion) of Trisenox.[385] According to the Press Release, the allegations continued from 2001 until 2005 when CTI sold Trisenox to another company who subsequently ended the off-label promotion campaign.[386] The government alleged that CTI aggressively marketed Trisenox to physicians for use in treating certain types of cancers "even though the company knew that the drug had no proven medical benefit in the treatment of those cancers…."[387] The Press Release also alleged that CTI used illegal kickbacks to induce physicians to prescribe Trisenox.[388]

Clinical

The FDA approved Trisenox on September 25, 2000 for patients who are refractory to, or have relapsed from, retinoid and anthracycline chemotherapy, the standard first-line treatment for acute promyelocytic leukemia ("APL"). A list of the

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[383] *Id*. ¶87.
[384] *Id.* ¶87.
[385] Press Release, Cell Therapeutics, Inc. to Pay United States $10.5 Million to Resolve Claims for Illegal Marketing of Cancer Drug, Department of Justice (Apr. 17, 2007).
[386] *Id*. at 1.
[387] *Id*. at 1.
[388] *Id*.

indications and off-label uses per drug as published in the AHFS from 1997 through 2010 is available upon request.

According to the 2007 Complaint, Trisenox is only indicated for treatment of 20 to 30% of APL patients who have relapsed from standard therapies (retinoid and anthracycline chemotherapy).[389] There are only about 1,000 patients diagnosed with APL each year. According to the Complaint, APL is a specific type of leukemia that affects about 10 to 15% of the approximately 10,000 patients diagnosed with acute myeloid leukemia (AML) in the United States each year.

Factual Allegations & Admissions [390]

Former employee, James Marchese, brought the Complaint against Cell Therapeutics after discovering the activities while employed from October 2000 through September 2002.[391] The Complaint alleges that Cell Therapeutics improperly marketed Trisenox for off-label uses, caused improper payments to physicians in the form of kickbacks, and failed to disclose side-effects.[392] The off-label allegations include promotion for the following unapproved indications: multiple myeloma (MM), myelodysplastic syndrome (MDS), chronic myeloid leukemia (CML), chronic lymphocytic leukemia (CLL), and AML.[393]

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[389] Corrected First Amended Complaint, United States of America ex rel. James Marchese v. Cell Therapeutics, Inc., Medcomm Solutions, Envision Pharma, Inc. and Amerisourcebergen Corp., No. 06-cv-0168 (W.D. WA.), ¶ 2.
[390] Corrected First Amended Complaint, United States of America ex rel. James Marchese v. Cell Therapeutics, Inc., Medcomm Solutions, Envision Pharma, Inc. and Amerisourcebergen Corp., No. 06-cv-0168 (W.D. WA.).
[391] *Id*. ¶ 10.
[392] *Id*. ¶9.
[393] *Id*. ¶ 66.

At a sales meeting held two months after receiving FDA approval to market Trisenox (November 2000), sales representatives were told that sales growth should be driven by off-label marketing.[394] Other regional and national sales meetings throughout the years also heavily emphasized off-label uses of Trisenox.[395] Additionally, the Complaint alleges that Cell Therapeutics organized Advisory Board meetings to reach physicians, and thereby promote off-label uses.[396]

After 2002, Cell Therapeutics hired an outside consulting firm to handle Advisory Board meetings in order to meet ACCME standards, but the Complaint alleges that Cell Therapeutics retained control over the content delivered by the outside firm at the meetings.[397]

The Complaint also alleges that Cell Therapeutics marketed to physicians who "rarely – if ever – prescribe Trisenox" for APL.[398] APL is generally treated at large academic research-based cancer treatment centers, but Cell Therapeutics targeted physicians at community hospitals.[399] According to the Complaint, unlike APL, more than three-fourths of MDS and AML patients are treated at community hospitals (both off-label uses of Trisenox).[400]

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[394] *Id*. ¶ 70. The Complaint cites verbiage such as: " Expand Trisenox business outside of APL…."; "Before we start selling in other areas, lets make sure we know what we are talking about"; "Reimbursement strategies in MM." Id. ¶ 70.
[395] *Id*. ¶¶ 71-73.
[396] *Id*. ¶¶ 76-80.
[397] *Id*. ¶ 85.
[398] *Id*. ¶89.
[399] *Id*. ¶88-89.
[400] *Id*. ¶ 90.

Cell Therapeutics also promoted the use of doses not approved. For instance, the indicated dosage is 0.15 mg.kg/day, but the dosages suggested by sales representatives to physicians were almost double this amount.[401] A sales training memo distributed to sales representatives stated that given a better understanding of the chemistry of Trisenox, sales representatives should encourage physicians to follow a 0.20 to 0.25 mg/kg/day dosing schedule.[402] The memo also stated "we have no data at the present time to support this dose and schedule."[403] The Complaint alleges that Cell Therapeutics also failed to inform doctors of side-effects caused by Trisenox, and misrepresented clinical data.[404]

Cell Therapeutics took advantage of the fact that the USPDI volume III listed MM and MDS as uses for Trisenox even though volume III simply lists orphan designations and is not the compendium used to determine clinically appropriate off-label uses.[405] The USPDI contains three volumes: volume I describes certain uses of drugs, including off-label uses that are accepted by research and other data; volume II lists the drugs and is intended to be a guide for patients; volume III lists drugs and special designations they possess such as orphan drug status. There is no literature or support for

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[401] *Id.* ¶¶ 93-95.
[402] *Id.* ¶ 94.
[403] *Id.* ¶ 94.
[404] *Id.* ¶¶ 98-109.
[405] *Id.* ¶ 165. Volume I lists drug information monographs and other information, including its accepted indications. Volume III contains the entire text of the FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations"- the Orange Book. This volume is a list of all drugs with an effective application on file and also includes exclusivity data and patent information.

using Volume III as a substitute for volume I's thorough review of appropriate drug uses based on evidence-based research.

Cell Therapeutics undertook a successful campaign to misrepresent what was stated in the USPDI to Medicare carriers in order for them to get approval for off-label uses that were not listed in volume I of the USPDI.[406] According to the Complaint, there was no published peer-reviewed study to support use in MM, or other off-label uses as of 2000 when Cell Therapeutics received approval for APL.[407] Cell Therapeutics employed a third party to handle off-label reimbursement, and talk directly with Medicare carriers unsure of whether off-label reimbursement was authorized.[408] Cell Therapeutics compensated the third party based, in part, on its handling of insurance verification, eligibility, and appeals.[409]

Mr. Marchese, the former employee of Cell Therapeutics who brought the suit assisted Cell Therapeutics in a scheme to get reimbursement from Medicare and other government programs for off-label uses.[410]

The Complaint also alleges that Cell Therapeutics improperly reimbursed physicians to attend meetings and dinners promoting Trisenox.[411] Cell Therapeutics also provided grants to physicians and medical facilities to "reward those physicians who demonstrated that they were advocates and active prescribers of Trisenox."[412]

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[406] *See id*. ¶¶ 173-184; 189.
[407] *Id*. ¶ 167.
[408] *Id*. ¶ 191-193.
[409] *Id*. ¶194.
[410] *Id*. ¶¶168-70.
[411] *Id*. ¶¶ 141-50.
[412] *Id*. ¶ 151.

4.1.12 Xyrem®—Jazz Pharmaceutical, Inc. (Orphan Medical)

Overview

According to the 2007 HCFAC Report, Jazz Pharmaceuticals, Inc., paid $20 million to resolve criminal and civil allegations relating to the illegal marketing practices of its wholly-owned subsidiary, Orphan Medical, Inc.[413] Orphan Medical Inc. pled guilty to felony misbranding, in violation of the FDCA in connection with its off-label promotion of Xyrem.[414]

Clinical

The FDA approved Xyrem on July 17, 2002 for the treatment of cataplexy (weak or paralyzed muscles) associated with narcolepsy (a neurological disorder that affects a person's ability to control sleep and wakefulness. A list of the indications and off-label uses per drug as published in the AHFS from 1997 through 2010 is available upon request.

Xyrem is commonly known as GHB, which is a controlled substance with a history of abuse. It is a central nervous system depressant that has extremely dangerous risks associated with its use including seizure, respiratory depression, and profound

[413] The Department of Health and Human Services and The Department of Justice Health Care Fraud and Abuse Control Program Annual Report for FY 2007, at 12 (Nov. 2008).
[414] *Id*.

decreases in level of consciousness, with instances of coma and death. GHB is a powerful and fast-acting central nervous system depressant that has been subject to abuse as a recreational drug and is classified by HHS as a "date rape" drug.

The number of people estimated to suffer from narcoleptic cataplexy is between 20,000 and 50,000 patients.[415]

When the FDA approved Xyrem in 2002, the FDA explained its previous ban on GHB products:

> In the early 1990s, GHB was marketed as a dietary supplement for many claimed purposes, including inducing sleep, releasing growth hormone, enhancing sexual activity and athletic performance, and relieving depression. It also gained favor as a recreational drug, and was used for date rape, because of its intoxicating effects.
>
> Many serious adverse events, including deaths, were reported with the use and misuse of the GHB containing products. As use increased, so did the adverse event reports. That prompted FDA to make several public announcements alerting consumers to the dangers surrounding GHB and similar products… [and led the FDA] to prevent their sale to consumers and any further illneses or deaths.[416]

The FDA authorized only one centralized pharmacy to distribute the drug so that prescribers and patients could only obtain the product through a single source.

Factual Allegations & Admissions

Former employee, Shelley Lauterbach brought the lawsuit on behalf of the United States of America and the States to recover damages and civil penalties for violations of

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[415] Compl ¶ 4.

[416] *Id*. ¶ 46 (quoting "Xyrem (Sodium Oxybate) Questions and Answers," FDA Center for Drug Evaluation and Research, published July 17, 2002, reprinted at www.fda.gov/cder/drug/infopage/xyrem.

the FCA.[417] The Complaint alleges that beginning in about 2003 and continuing through the date of the Complaint (January 2005), Orphan promoted Xyrem for off-label uses.[418] The off-label marketing and promotional campaign included: speaker events saturated with off-label messages; generous speaker fees to off-label prescribing physicians; grants that provided physicians with kickbacks as an inducement or reward for prescribing Xyrem off-label; targeted sales calls on prescribing physicians by field representatives to reinforce the off-label message and translate it into increased Xyrem sales.[419] Some of the off-label uses included: fibromyalgia, insomnia, non-specific sleep disorders, fatigue, and psychiatric disorders.[420]

The Complaint alleges that Dr. Peter Gleason (named as a party) was a centerpiece of Orphan's off-label speaker campaign.[421] His talks also included explaining how to defraud private and public healthcare insurers by falsifying the diagnosis on reimbursement claim forms in order to conceal the off-label nature of the prescription.[422]

The Complaint alleges that sales of Xyrem have nearly doubled since the illegal campaign began.[423]

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[417] Complaint, United States of America et al. ex rel. Shelley Lauterbach v. Orphan Medical Inc., and Dr. Peter Gleason, No. 05-cv-00387, Jan. 24, 2005 (E.D.N.Y.).
[418] *Id.* ¶ 2.
[419] *Id.* ¶ 5. Orphan paid Dr. Gleason hundreds of thousands of dollars to speak at hundreds events, and his talks were saturated with off-label uses of Xyrem. Id.
[420] *Id.* ¶ 6.
[421] *Id.* ¶¶ 6, 85-104.
[422] *Id.* ¶ 6.
[423] *Id.* ¶ 7.

At a national sales meeting in January 2004, Xyrem sales representatives were told to promote Xyrem for off-label uses, and that Dr. Gleason would come and "work magic" in the sales representatives territories to encourage and promote off-label uses.[424] According to the Relator, her manager informed her that management wanted to sell the company, and therefore needed increased sales of Xyrem.[425] When Relator first began working for Orphan, her quota was to enroll 9 new patients per quarter onto Xyrem, and at the end of 2004 her new patient quotas increased to 70 patients per quarter.[426] Given the limited FDA-approved use, the new quotas set for sales representatives in 2004 could only be achieved by heavily promoting Xyrem for off-label uses.[427]

The kickback violations revolve around paying physicians to speak about off-label uses of Xyrem. In particular, Dr. Gleason received hundreds of thousands of dollars to speak about using Xyrem for fibromyalgia, insomnia, excessive daytime sleepiness, fatigue, and psychiatric disorders.[428] Dr. Gleason was paid to travel to different parts of the country to assist the sales representatives in achieving their quotas by confirming the value of Xyrem for off-label uses.[429] Dr. Gleason also taught other physicians which billing codes were most likely to pass scrutiny with insurers and be reimbursed.[430]

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[424] *Id*. ¶¶ 65-70.
[425] *Id*. ¶ 72.
[426] *Id*. ¶¶ 77-78.
[427] *Id*. ¶¶ 78-80.
[428] *Id*. ¶ 85.
[429] *Id*. ¶¶ 85-88.
[430] *Id*. ¶ 91.

Several other physicians are also listed in the Complaint as speakers who were paid by Orphan to speak about the value of Xyrem for off-label uses.[431]

4.1.13 Cardizem® LA—Biovail

Overview

On May 16, 2008, the District of Massachusetts announced that Biovail Pharmaceuticals, Inc. agreed to plead guilty to conspiracy and kickback charges and to pay a criminal fine of $22,243,590 in connection with its promotion of Cardizem LA.[432] Biovail also agreed to pay $2.4 million to settle civil claims.[433] Both the civil claims and criminal fine involved charges Biovail improperly paid doctors and other prescribers up to $1,000 to recommend Cardizem.[434]

Clinical

The FDA approved Cardizem LA on February 6, 2003 for the treatment of hypertension alone or in combination with other antihypertensive medications. In January 2001 Biovail acquired the Cardizem line of drugs from another company. In

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[431] *Id*. ¶¶ 105-33.
[432] Press Release, New Jersey Company Agrees To Plead Guilty To Kickbacks And Conspiracy Charges And Pay More Than $22 Million Dollars In Criminal Fines, Department of Justice, United States Attorney Michael J. Sullivan District of Massachusetts (May 16, 2008).
[433] Press Release, Biovail Enters Guilty Plea, Signs Civil Agreement, Reuters (Sept. 14, 2009).
[434] *Id.*

2003, Medicaid paid in excess of $3 million in reimbursement for prescriptions for Cardizem L.A. nationwide.[435] A list of the indications and off-label uses per drug as published in the AHFS from 1997 through 2010 is available upon request.

Factual Allegations & Admissions

The lawsuit involved paying physicians and other prescribers up to $1,000 for enrolling between 11 to 15 patients in a program causing patients to fill prescriptions for Cardizem LA in violation of the Anti-kickback Act.[436] Email correspondence provided in the Complaint from the Biovail Product Manager to higher level sales and marketing managers stated: "To date, a total of 89,092 Rxs have been recorded for Cardizem LA, as of June 6th 2003. Congratulations once again on all the success the PLACE Program is having in driving prescriptions and market share!!"[437] From March 2003 through at least December 2003, the PLACE program was used to induce prescribers to prescribe Cardizem LA.

4.1.14 Baycol®—Bayer

Overview

On January 23, 2007, the Attorney General for the state of Florida announced that Bayer Corporation entered into a settlement agreeing to pay $8 million to resolve allegations of improper marketing of Baycol. Florida Attorney General Bill McCollum

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[435] *Id.* ¶ 39.
[436] Information, United States of America v. Biovail Pharmaceuticals Inc., 08-cr-10124, May 19, 2008 (D.Mass.). p. Conspiracy to Offer and pay Illegal Remuneration to Physicians (18 U.S.C. § 371) and Offers of Remuneration to Physicians (42 U.S.C. § 1320a-7(b)(b)(2).
[437] *Id.* ¶ 26.

announced the settlement involving Florida and 29 additional states. The settlement was part of a consumer protection enforcement action initiated over concerns that Bayer failed to adequately disclose safety risks associated with Baycol.

Baycol was withdrawn from the prescription drug market in August 2001 after post marketing studies showed potential health hazards particularly in combination with another cholesterol-lowering drug. The investigation, initiated by the states in 2004, alleged that while Bayer informed the US Food and Drug Administration about the adverse effects observed in post-marketing studies, the company failed to warn consumers or change its marketing practices.

Clinical

The FDA approved Baycol on June 26, 1997 as an adjunct to diet to reduce elevated Total-C, LDL-C, Apo B, and TG and to increase HDL-C levels in patients with primary hypercholesterolemia and mixed dyslipidemia (Fredrickson Types IIa and IIb) when the response to dietary restriction of saturated fat and cholesterol and other non-pharmacological measures alone have be inadequate. A list of the indications and off-label uses per drug as published in the AHFS from 1997 through 2010 is available upon request. Baycol was withdrawn from the market on August 8, 2001. U.S. sales of Baycol were approximately $290 million in 2000 and were projected to reach $591 million in 2001. More than 2 million patients are estimated to have used Baycol when it was on the market.[438]

Factual Allegations & Admissions

[438] Compl. ¶41

A former employee of Bayer brought the lawsuit to recover damages and civil penalties on behalf of the United States of America for marketing activities in violation of the FCA.[439] The Complaint alleged that from September 1998 through August 8, 2001, Bayer engaged in "improper and unlawful marketing strategies" through illegal kickbacks and misbranding in violation of the FCA and Anti-Kickback statute.[440] The Complaint alleged that Bayer downplayed safety concerns and strengthened the efficacy perception of Baycol through marketing efforts, resulting in misbranding of Baycol.[441]

For instance, beginning summer of 2000, Bayer used the following statement as support for Baycol's efficacy: "Baycol 0.8 mg gets 84% of patients to NCEP goal."[442] However, the clinical trial that Bayer used to support this statement included many patients who were already at NCEP goal and/or not eligible for drug treatment using NCEP guidelines.[443]

Bayer launched the 0.8 mg dose in July 2000, and although all FDA approved documentation indicated patients should start at 0.4 mg and titrate up to 0.8 mg, informal and oral communications by Bayer sales representatives' encouraged the use of the higher, 0.8 mg, as the starting dose.[444] For example, at breakout sessions during a Bayer global marketing meeting for representatives, statements were made suggesting that

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[439] Amended Complaint, United States of America et al. ex rel. Laurie Simpson v. Bayer Healthcare d/b/a Bayer Healthcare Pharmaceuticals; Bayer Pharmaceuticals Corp.; Bayer Corp.; and Bayer A.G., No. 06-cv-4796, Mar. 31, 2008 (D. N.J.).
[440] *Id.* ¶¶ 6, 10.
[441] *Id.* ¶ 88.
[442] *Id.* ¶ 88.
[443] *Id.* ¶ 89.
[444] *Id.* ¶¶ 96-98.

Baycol was superior or substantially safer than Lipitor.[445] The Complaint alleges that Bayer omitted or downplayed risk and adverse incidents associated with Baycol and implied Baycol had comparable efficacy to Lipitor.[446]

The Complaint alleges that the whistleblower (a sales representative) first learned in late Spring 2001 that there were a significant number of deaths that were believed to be caused by use of Baycol.[447] According to the former employee, senior Bayer personnel knew of the deaths long before but failed to disclose safety problems.[448] By failing to provide relevant safety information to sales representatives and other marketing employees, representatives failed to provide important safety information to prescribers while emphasizing the benefits of the product.[449]

4.1.15 Actiq, Gabitril, Provigil—Cephalon

Overview

On September 29, 2008, the Department of Justice announced that Cephalon Inc. entered a criminal plea and paid $425 million to resolve claims that it promoted Actiq, Gabitril, and Provigil for off-label uses.[450] The plea agreement with the United States included Cephalon agreeing to pay $50 million to resolve the criminal allegations, of which $40 million will be applied to a criminal fine, and $10 million will be applied as

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[445] *Id.* ¶ 104.
[446] *Id.* ¶ 135.
[447] *Id.* ¶ 132.
[448] *Id.* ¶ 132.
[449] *Id.* ¶ 132.
[450] Press Release, Biopharmaceutical Company, Cephalon, to Pay $425 Million & Enter Plea to Resolve Allegations of Off-Label Marketing, Department of Justice (Sept. 29, 2008).

substitute assets to satisfy the forfeiture obligation.[451] For the civil settlement, Cephalon paid $375 million, plus interest, to resolve False Claims Act allegations arising from claims to Medicaid, Medicare and other federal programs, including TRICARE, the Federal Employees Health Benefits program, the Postal Worker's Compensation Program, the Federal Employees Compensation Act Program, the Every Employees Occupational Illness Compensation Program, Department of Veterans Affairs, Defense Logistics Agency, Bureau of Prisons and the Public Health Service Entities.[452] The Medicaid programs of the following states will share $116 million of the civil settlement: California, Delaware, Florida, Hawaii, Illinois, Louisiana, Massachusetts, Nevada, New Hampshire, New Mexico, Texas, Tennessee, Virginia, and the District of Columbia.[453]

From 2001 and 2006, Cephalon allegedly promoted Actiq for non-cancer patients to use for such maladies as migraines, sickle-cell pain crises, injuries, and in anticipation of changing wound dressings or radiation therapy.[454] From 2001 to 2005, Cephalon allegedly promoted Gabitril as a remedy for anxiety, insomnia, and pain.[455] In 2005, following reports of seizures in patients taking Gabitril who did not have epilepsy, the FDA required Cephalon to send a warning letter to doctors advising them of the connection between off-label Gabitril use and seizures.[456] According to the Press

[451] *Id.*
[452] *Id.*
[453] *Id.*
[454] *Id.*
[455] *Id.*
[456] *Id.*

Release, Cephalon ceased promotion of the drug after the FDA mandated that Cephalon distribute a warning letter to doctors.[457]

From 2001 through 2006, Cephalon allegedly promoted Provigil as a non-stimulant drug for the treatment of sleepiness, tiredness, decreased activity, lack of energy, and fatigue.[458] In 2002, the FDA sent Cephalon a warning letter not to continue to promote Provigil off-label.[459] The whistleblower received $46,469,978 from the federal share of the settlement amount.[460] The HHS Inspector General and Cephalon have entered into a five year Corporate Integrity Agreement.[461]

Clinical

The FDA approved Gabitril on September 30, 1997 as an adjunctive therapy for the treatment of partial seizures in adults and children twelve years and older. The FDA approved Actiq on November 4, 1998 for the management of breakthrough cancer pain in patients with malignancies who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain. The original Actiq label included a black box warning to prescribers advising them not to use Actiq for acute or postoperative pain, in opioid non-tolerant patients, or in children. The warning also stated: "Actiq is intended to be used only in the care of cancer patients and only by oncologists and pain specialists who are knowledgeable of and skilled in the use of

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[457] *Id.*
[458] *Id.*
[459] *Id.*
[460] *Id.*
[461] *Id.*

Schedule II opioids to treat cancer pain."[462] The FDA approved Provigil on December 24, 1998 to improve wakefulness in patients with excessive daytime sleepiness associated with narcolepsy. A list of the indications and off-label uses per drug as published in the AHFS from 1997 through 2010 is available upon request.

Factual Allegations & Admissions

The lawsuit was originally filed by a former employee of Cephalon. At the time of the Complaint, Lucia Paccione had worked as a medical sales representative, area trainer, and institutional representative at various times over the past 8 ½ years.[463] With respect to Gabitril, the Complaint alleges that Cephalon targeted psychiatrists and pain clinics as the primary markets for Gabitril despite the fact that treatment of partial seizures is not something generally treated by a psychiatrist or a pain clinic.[464] The Complaint alleges that Cephalon marketed Gabitril for off-label uses such as anxiety, mood disorders, and pain.[465] Sales representatives were instructed to promote Gabitril off-label as an alternative to benzodiazepines in pain clinics.[466]

In 2001, after Cephalon purchased the rights for Gabitril from Abbott, Cephalon began an "even more aggressive off-label promotion campaign" to market Gabitril to psychiatrists.[467] Based on the approved indication, psychiatrists had no known use for the FDA approved purpose of Gabitril.[468] Cephalon instructed sales representatives to

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[462] Actiq label dated November 11, 1998 available at www.fda.gov.
[463] Complaint Lucia Paccione v. Cephalon Inc., No. 03-cv-06268, ¶ 15.
[464] *Id.* ¶29.
[465] *Id.* ¶29.
[466] *Id.* ¶ 42.
[467] *Id.* ¶¶43, 44.
[468] *Id.* ¶44.

market Gabitril to psychiatrists for pain, mood disorders, and anxiety.[469] The relator, Ms. Paccione's, direct supervisor directed her to concentrate her marketing and promotion on psychiatrists.[470] Some of the activities included providing large volumes of samples with psychiatrists for off-label uses, and a small case study performed by Dr. Gruner on the use of Gabitril for depression.[471]

The Complaint states that Ms. Paccione was uncomfortable with marketing to psychiatrists, and her supervisors criticized her for not instructing psychiatrists that the maximum dosage for various off-label uses is 32-56 milligrams.[472] One writing she received from her supervisor included the following: "persuading physicians to use Gabitril as a substitute for benzodiazepines when treating anxiety 'is an area of incredible opportunity for potential sales that needs to be understood if you are going to drive the sales as required.'"[473]

With respect to Actiq, the Complaint alleges that Cephalon originally targeted oncologists, but with disappointing first year sales, switched to those within the areas of physical rehabilitation, primary care physicians, and also neurologists who treat severe headaches.[474] The Complaint alleges off-label promotional initiatives regarding Actiq and Provigil, but does not provide specifics about the two drugs.[475]

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[469] *Id.* ¶ 47.
[470] *Id.* ¶ 80.
[471] *Id.* ¶60. Dr. Gruner has received honoria from Cephalon in exchange for speaking on the benefits of Gabitril.
[472] *Id.* ¶ 82.
[473] *Id.* ¶ 84.
[474] *Id.* ¶¶ 31, 32.
[475] *Id.* ¶¶ 67, 76.

4.1.16 Zyprexa—Eli Lilly & Co. II

Overview

On January 15, 2009 the Department of Justice announced that Lilly agreed to pay $ 1.415 billion to resolve allegations that it illegally promoted olanzapine for unapproved uses.[476] At the time, the settlement represented the largest individual criminal corporate crime in United States history.[477] Lilly pled guilty to a misdemeanor criminal charge.[478] Lilly admitted that between September 1999 and March 31, 2001, the company promoted Zyprexa (olanzapine) in elderly populations for treatment of dementia, including Alzheimer's dementia.[479] The civil settlement represents $ 800 million of the total to resolve the *qui tam* lawsuits.[480]

Clinical

The FDA approved Zyprexa (olanzapine) on September 30, 1996[481] for the treatment of manifestations of psychotic disorders. As of May 2010, oral olanzapine was indicated: (1) for the treatment of schizophrenia in ages 13 and up, (2) for the acute treatment of manic or mixed episodes associated with bipolar I disorder and maintenance treatment of bipolar I disorder, and (3) for the treatment of manic or mixed episodes

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[476] Press Release, Department of Justice, Eli Lilly and Company Agrees to Pay $1.415 Billion to Resolve Allegations of Off-label Promotion of Zyprexa: $515 Million Criminal Fine Is Largest Individual Corporate Criminal Fine in History; Civil Settlement up to $800 Million (Jan. 15, 2009), http://www.justice.gov/opa/pr/2009/January/09-civ-038.html [hereinafter Lilly-II Press Release].
[477] *Id.*
[478] *Id.*
[479] *Id.* at 2.
[480] *Id.*
[481] Orange Book, www.fda.gov.

associated with bipolar I disorder as an adjunct to lithium or valproate.[482] A list of the indications and off-label uses per drug as published in the AHFS from 1997 through 2010 is available upon request.

Factual Allegations & Admissions

The lawsuit requested damages and civil penalties arising from false statements made by Lilly in violation of the FCA.[483] Former employee, Joseph Faltaous, who worked as a Neuroscience Sales Specialist for Eli Lilly filed the lawsuit. The Complaint alleges that Eli Lilly (Lilly) marketed Zyprexa to children, an off-label use.[484] Lilly "mandated that each representative call on ten pediatric psychiatrists every month."[485] On May 30, 2002, the FDA granted a waiver to Lilly allowing Lilly to forego conducting pediatric studies on children.[486] The granting of the waiver suggests that Lilly did not intend to market Zyprexa to children "either because Lilly knew it was unsafe in that population or because Lilly knew that doctors would not prescribe it to that population."[487] After the FDA granted the waiver, Lilly mandated to sales representatives that they market to pediatric psychiatrists.[488]

The Complaint further alleges that Lilly mandated to representatives to encourage physicians to prescribe Zyprexa in starting doses in excess of 30 mgs, and oftentimes as

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[482] MICROMEDEX® Healthcare Series, Physician's Desk Reference (PDR), Zyprexa® drug profile.
[483] *Id.* ¶ 14.
[484] *Id.* ¶10.
[485] *Id.* ¶10.
[486] *Id.* ¶ 10.
[487] *Id.* ¶10.
[488] *Id.* ¶ 10.

high as 60 mgs Zyprexa indicated for doses up to 20 mg.[489] Lilly also paid physicians about $4000 for every presentation given to promote higher doses.[490]

At least one of the civil complaints alleged that Lilly promoted the use of Zyprexa (olanzapine) in children, an unapproved use.[491] Lilly's alleged efforts were especially troubling because Lilly requested, and the FDA granted a waiver of the requirements to conduct pediatric studies on children.[492] The Complaint further alleged that sales representatives promoted Zyprexa (olanzapine) for dosages many times above the approved labeling.[493] Despite literature demonstrating that doses about 10 mg do not improve health outcomes, Lilly encouraged representatives to promote Zyprexa (olanzapine) to physicians at doses in excess of 30 mg and as high as 60 mg.[494] Zyprexa (olanzapine) only comes in oral dosages up to 20 mg, meaning in order to increase the dose beyond 20 mg, a patient would need to take more than one tablet a day. When patients take more than one tablet per day, the number of tablets that the patient needs to buy every month increases, thereby increasing revenue to Lilly. The Complaint also alleged that Lilly paid excessive sums to physicians who would speak about 60 mg dosages of olanzapine at meetings and other events.[495] Other off-label promotional

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[489] *Id.* ¶ 11.
[490] *Id.* ¶11.
[491] Second Amended Complaint, United States *ex rel*. Joseph Faltaous v. Eli Lilly & Co., (06-cv-2909) (E.D. Pa. July, 10 2008), ¶ 12.
[492] *Id.*
[493] *Id.* ¶ 11.
[494] *Id.*
[495] Complaint Lilly II, ¶ 11 (stating that physicians were paid about $ 4,000 for every presentation given to promote higher dosages of olanzapine). The presentations lasted about 45 minutes to an hour.

allegations included promoting olanzapine for use in treating anxiety, irritability, depression, nausea, Alzheimer's, and other mood disorders.[496]

Lilly made over $30 billion in revenue on olanzapine prior to the settlement. The medication provided Lilly with $36 billion in revenue from 2000 to 2008. Lilly's revenue garnered from olanzapine is 25 times the total penalties Lilly paid to resolve off-label allegations. Companies regard the risk of multimillion-dollar penalties as just another cost of doing business, says Lon Schneider, a professor at the University of Southern California's Keck School of Medicine in Los Angeles. In 2006, he led a study for the National Institute of Mental Health of off-label use of drugs, including Zyprexa, for the treatment of Alzheimer's disease. "There's an unwritten business plan," he says. "They're drivers that knowingly speed. If stopped, they pay the fine, and then they do it again."[497]

4.1.17 Bextra, Geodon, Zyvox, Lyrica—Pfizer Co. III (Pharmacia & Upjohn II)

Overview

On September 2, 2009, the Department of Justice announced that Pfizer Inc. and its subsidiary Pharmacia & Upjohn Company Inc. (hereinafter together "Pfizer") agreed to pay $2.3 billion, to resolve criminal and civil liability arising from the illegal

[496] Lilly-II Press Release at 3.
[497] David Evans, Pfizer Broke the Law by Promoting Drugs for Unapproved Uses, Bloomberg (Nov. 9, 2009), http://preview.bloomberg.com/apps/news?pid=newsarchive_en10&sid=a4yV1nYxCGoA.

promotion of certain pharmaceutical products. [498] Pfizer acquired Pharmacia & Upjohn, Inc. in 2003. Pharmacia & Upjohn Company agreed to plead guilty to a felony violation of the FDCA for misbranding Bextra by promoting it for off-label uses.[499] "Pfizer promoted the sale of Bextra for several uses and dosages that the FDA specifically declined to approve due to safety concerns."[500] The company paid a criminal fine of $1.195 billion for the illegal promotion of Bextra, the largest criminal fine ever imposed in the United States for any matter.[501] Pharmacia & Upjohn also forfeited $105 million, making the total criminal amount $1.3 billion.[502] "From 2002 through April 2005, Pfizer used false and misleading claims of safety and efficacy to promote Bextra for unapproved uses and for dosages above the approved level."[503]

Pfizer also agreed to pay $1 billion to resolve allegations under the civil False Claims Act that the company promoted four drugs off-label: Bextra, Geodon, Zyvox, and Lyrica, and caused false claims to be submitted to government health care programs for uses that were not medically accepted indications.[504] The civil settlement also resolved allegations that "Pfizer paid kickbacks to health care providers to induce them to

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[498] Press Release, Justice Department Announces Largest Health Care Fraud Settlement in its History, Department of Justice, U.S. Department of Health and Human Services (Sept. 2, 2009).
[499] *Id.*
[500] *Id.*
[501] *Id.*
[502] *Id.*
[503] Pfizer Fact Sheet: Pfizer to pay $2.3 billion to resolve criminal and civil health care liability relating to fraudulent marketing and the payment of kickbacks, STOPMedicareFraud.gov, U.S. Department of Health and Human Services and U.S. Department of Justice, available at STOPMedicareFRAUD.gov (last visited Sept. 28, 2010).
[504] *Id.*

prescribe these, as well as other, drugs."[505] The federal share of the civil settlement was $668,514,830, and the state Medicaid share was $331,485,170.[506]

Pfizer also agreed to enter into an "expansive" CIA with the Office of Inspector General of the Department of Health and Human Services.[507] Six whistleblowers received payments totaling more than $102 million from the federal share of the civil recovery.[508]

> The size and seriousness of this resolution, including the huge criminal fine of $1.3 billion, reflect the seriousness and scope of Pfizer's crimes, said Mike Loucks, acting U.S. Attorney for the District of Massachusetts. Pfizer violated the law over an extensive time period. Furthermore, at the very same time Pfizer was in our office negotiating and resolving the allegations of criminal conduct by its then newly acquired subsidiary, Warner-Lambert, Pfizer was itself in its other operations violating those very same laws. Today's enormous fine demonstrates that such blatant and continued disregard of the law will not be tolerated.
>
> Health care fraud has a significant financial impact on the Postal Service. This case alone impacted more than 10,000 postal employees on workers' compensation who were treated with these drugs, said Joseph Finn, Special Agent in Charge for the Postal Service's Office of Inspector General. Last year the Postal Service paid more than $1 billion in workers' compensation benefits to postal employees injured on the job.

The civil settlement included:

- Illegally promoting the drugs Bextra, Geodon, Zyvox, and Lyrica for uses not approved by the FDA and that were not medically-accepted indications for which the United States and state Medicaid programs provided coverage;

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[505] *Id.*
[506] *Id.*
[507] *Id.*
[508] *Id.*

- Making and disseminating unsubstantiated and false representations about the safety and efficacy of Bextra, Geodon, Zyvox, and Lyrica;
- Paying kickbacks to health care providers to induce them to prescribe Bextra, Geodon, Zyvox, and Lyrica;
- Paying kickbacks to health care providers in connection with its marketing of nine other drugs: Aricept, Celebrex, Lipitor, Norvasc, Relpax, Viagra, Zithromax, Zoloft, and Zyrtec (Kickback Drugs)[509]

Allocation of the civil settlement amount by drug was: Bextra: $502,524,316; Geodon: $301,462,065; Zyvox: $97,945,019; Lyrica: $48,223,886; Kickback Drugs: $49,844,714. Thus, the allocation to Bextra is approximately $1,802,524,316 (civil settlement amount for Bextra, $502,524,316, plus the criminal settlement amount for Bextra of $1.3 billion).

Clinical

The FDA approved Bextra on November 16, 2001 for the relief of the signs and symptoms of osteoarthritis and adult rheumatoid arthritis and for the treatment of primary dysmenorrheal. A list of the indications and off-label uses per drug as published in the AHFS from 1997 through 2010 is available upon request. On April 7, 2005, the FDA asked that Pfizer voluntarily withdraw Bextra from the U.S. market because the Agency concluded that the overall risk versus benefit profile of Bextra was unfavorable.[510] The

[509] *Id*.
[510] FDA Alert: Information for Healthcare Professionals: valdecoxib (marketed as Bextra), dated April 7, 2005, available at www.fda.gov (last visited Aug. 22, 2012).

FDA provided the following data assessment in the announcement requesting withdrawal of Bextra:

> Bextra has been demonstrated to be associated with an increased risk of serious adverse CV events in two short-term trials in patients immediately post-operative from coronary artery bypass graft (CABG) surgery.
> Bextra is a sulfonamide and already carries a boxed warning in the package insert for serious and potentially life-threatening skin reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme). The reporting rate to FDA's spontaneous reporting system for these serious skin reactions is significantly greater for Bextra than other COX-2 selective agents. The risk of these serious skin reactions in individual patients is unpredictable, occurring in patients with and without a history of sulfa allergy, and after both short- and long term use.
> To date, there have been no studies that demonstrate an advantage of Bextra over other NSAIDs that might offset the concern about these serious skin risks, such as studies that show a GI safety benefit, better efficacy compared to other products, or efficacy in a setting of patients who are refractory to treatment with other products.[511]

Factual Allegations & Admissions

A former employee, John Kopchinski brought the lawsuit against Pfizer and Pharmacia in Massachusetts.[512] The Massachusetts Complaint request damages and civil penalties on behalf of the United States of America and 21 states for Pfizer causing thousands of false claims to be made on federal and state health care programs resulting from the improper promotion of the drug Bextra for off-label uses.[513]

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[511] FDA Alert: Information for Healthcare Professionals: valdecoxib (marketed as Bextra), dated April 7, 2005, available at www.fda.gov (last visited Aug. 22, 2012).
[512] Third Amended Complaint, United States of America et al. ex rel. John Kopchinski v. Pfizer and Pharmacia Corp., No. 05-cv-12115-RCL, Dec. 22, 2008 (D. Mass).
[513] Complaint at page 3-4.

4.1.18 Celexa and Lexapro—Forest Labs.

Overview

On September 15, 2010 the Department of Justice announced that Forest Pharmaceuticals Inc., a subsidiary of Forest Laboratories Inc., agreed to pay $313 million and plead guilty to charges related to obstruction of justice, distribution of an unapproved new drug (Levothroid), and off-label promotion (Celexa for use in treating children and adolescents suffering from depression).[514] The False Claims Act Complaint also alleges that Forest engaged in off label promotion of Lexapro, which at the time[515] also lacked any approval for pediatric uses.[516] As part of the civil settlement, the federal government received more than $88 million and the states through Medicaid more than $60 million.[517] The whistleblowers received about $14 million from the federal share of the settlement.[518]

As part of the settlement, Forest Laboratories entered into a five year Corporate Integrity Agreement.[519] Forest is subject to mandatory exclusion if it materially breaches the CIA, or to monetary penalties for less significant breaches.[520]

Clinical

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[514] Press Release, Drug Maker Forest Pleads Guilty; To Pay More Than $313 Million To Resolve Criminal Charges and False Claims Act Allegations, Department of Justice, Office of Public Affairs (Sept. 15, 2010).
[515] The FDA approved Lexapro for major depressive disorder in adolescents, 12 to 17 years old on March 19, 2009.
[516] *Id.* at 2.
[517] *Id.* at 2.
[518] *Id.* at 2.
[519] *Id.* at 2.
[520] *Id.* at 2.

The FDA approved Celexa on April 27, 2000 for the treatment of depression. The FDA approved Lexapro on August 14, 2002 for the treatment of major depressive disorder. The FDA approved Levothroid on October 24, 2002 for the following indications: as replacement or supplemental therapy in congenital or acquired hypothyroidism of any etiology, except transient hypothyroidism during the recovery phase of subacute thyroiditis; specifically primary (thyroidal), secondary (pituituary), and tertiary (hypothalamic) hypothyroidism and subclinical hypothyroidism; and the treatment or prevention of various types of euthyroid goiters, including thyroid nodules, subacute and chronic lymphocytic thyroiditis (Hashimoto's thyroiditis), multinodular goiter and as an adjunct to surgery and radioiodine therapy in the management of thyrotropin-dependent-well-differentiated thyroid cancer. A list of the indications and off-label uses per drug as published in the AHFS from 1997 through 2010 is available upon request.

Factual Allegations & Admissions

Several lawsuits were filed in this matter. One lawsuit, filed by Dr. Piacentile, participated in an undercover investigation to secure admissions from physicians and pharmaceutical sales representatives regarding off-label allegations.[521] The Complaint specifically relates to the off-label promotion of Celexa. The Complaint alleges that Forest marketing personnel developed a scheme intended to improperly influence

[521] Complaint USA, et al ex rel. Joseph Piacentile, No. 05-cv-10201, ¶ 7.

prescribers to use Celexa by showering prescribers with lavish trips, honoraria and programs.[522]

The criminal information and another False Claims Act complaint filed by the United States alleged that Forest Pharmaceuticals promoted Celexa for unapproved pediatric use.[523] Despite approval only for adult depression, Forest Pharmaceuticals promoted Celexa for use in treating children and adolescents suffering from depression.[524] The government alleged that Forest publicized and circulated the positive results of a double-blind, placebo-controlled Forest study on the use of Celexa in adolescents while, at the same time, Forest failed to discuss the negative results of a contemporaneous double-blind, placebo-controlled European study on the use of Celexa in adolescents.[525]

The government also alleged that Forests' off-label promotion consisted of various sales techniques, including directing its sales representatives to promote pediatric use of Celexa in sales calls to physicians who treated children and adolescents, and hiring outside speakers to talk to pediatricians about the benefits of prescribing Celexa to children and teens.[526] The allegations against Forest also involved illegal marketing conduct in connection with Lexapro, which, at the time, also lacked any approvals for pediatric use.

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[522] Complaint at ¶ 22.
[523] Press Release, Drug Maker Forest Pleads Guilty; To Pay More Than $313 Million To Resolve Criminal Charges and False Claims Act Allegations, Department of Justice, Office of Public Affairs (Sept. 15, 2010).
[524] *Id.*
[525] *Id.*
[526] *Id.*

The government also alleged that Forest used illegal kickbacks to induce physicians and others to prescribe Celexa and Lexapro.[527] Kickbacks allegedly included cash payments disguised as grants or consulting fees, expensive meals and lavish entertainment. From 1998 to 2002 Celexa represented Forest's greatest source of income.[528]

4.1.19 Seroquel—Astra Zeneca

Overview

On April 27, 2010, the Department of Justice announced that AstraZeneca LP and AstraZeneca Pharmaceuticals LP paid $520 million to resolve allegations of off-label marketing of Seroquel in violation of the False Claims Act and Food, Drug, and Cosmetics Act.[529] The United States also contends that AstraZeneca violated the federal Anti-Kickback Statute by offering and paying doctors as ghostwriters, and to perform lectures on unapproved uses.[530] The federal government received $301,907,007 and the states through Medicaid received $218,092,993 of the civil settlement.[531] The settlement resolved false claims for payment from Medicaid, Medicare, TRICARE programs, the Department of Veteran's Affairs, Federal Employee Health Benefits Program, and the Bureau of Prisons.[532]

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[527] *Id.*
[528] Complaint at ¶ 8.
[529] Press Release, Pharmaceutical Giant AstraZeneca to Pay $520 Million for Off-label Drug Marketing, Department of Justice, Office of Public Affairs (Apr. 27, 2010).
[530] *Id.* at 2.
[531] *Id.* at 1.
[532] *Id.* at 1.

In March 2006, AstraZeneca brought certain conduct to the attention of the government, and cooperated in the investigation of the allegations in this settlement.[533] As part of the settlement, AstraZeneca entered into a five-year Corporate Integrity Agreement.[534] The Press Release states that AstraZeneca is subject to exclusion from federal health care programs if they materially breach the CIA and subject to monetary penalties for less significant breaches.

According to the DOJ Press Release, the illegal marketing activity occurred from January 2001 through December 2006.[535] The allegations included specific acts such as: marketing targeted at doctors who do not typically treat schizophrenia and bipolar disorder, improper conduct with respect to company-sponsored continuing medical education programs, recruiting doctors to serve as ghostwriters for articles, the use of studies and articles written by ghostwriters as the basis for promotional messages about unapproved uses, and violations of the Anti-Kickback Statute by offering and paying illegal remuneration to doctors it recruited to serve as authors of articles written by AstraZeneca and its agents about the unapproved uses of Seroquel.[536]

Clinical

The FDA approved Seroquel on September 26, 1997 for the treatment of manifestations of psychotic disorders. A list of the indications and off-label uses per drug as published in the AHFS from 1997 through 2010 is available upon request.

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[533] *Id.* at 2.
[534] *Id.* at 2.
[535] *Id.* at 1.
[536] *Id.* at 2.

Factual Allegations & Admissions

A former employee, James Wetta, brought the lawsuit against [537] AstraZeneca to recover damages and civil penalties on behalf of the United States of America arising from off-label promotion of the drug Seroquel causing the submission of false claims to the government.[538] Mr. Wetta worked as a sales representative for AstraZeneca.[539] The timeframe alleged for violations of the FCA were from at least sometime in 2002 and continuing to the present.[540] The Complaint alleges that sometime between January and February 2004, Mr. Wetta first learned of AstraZeneca's national sales program to aggressively market Seroquel to the elderly, children, and prisoners in a manner not approved by the FDA.[541] The off-label allegations, include, but are not limited to the following unapproved uses: 1) anger management; 2) dementia; 3) post-traumatic stress syndrome; 4) mood disorders; 5) refractory depression; 6) Parkinson's disease; and 7) cognitive dysfunction, hostility, aggression and agitation in children.[542]

The allegations within the Complaint include distributing memos to sales representatives about off-label uses of Seroquel[543], using monthly newsletters that describe how sales representatives might bypass nursing home OBRA regulations in

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[537] Fifth Amended Complaint, United States of America et al. *ex rel.* James Wetta v. AstraZeneca Corp., No. 04-cv-3479, Apr. 27, 2010 (E.D. Pa.).
[538] *Id.*
[539] *Id.* ¶ 9.
[540] *Id.* ¶ 95.
[541] *Id.* ¶ 11.
[542] *Id.* ¶ 15.
[543] *Id.* ¶¶ 31-34.

promoting Seroquel[544], paying physicians to assist AstraZeneca in marketing Seroquel to pediatric patients[545], and promoting Seroquel in detention facilities as "first line agent for aggressive patients."[546]

AstraZeneca also paid another physician about $175,000 in 2003 for CME lectures on greater than indicated titration doses of Seroquel.[547] For instance, call notes from two sales representatives described this physician as recommending doses of up to 1200 mg per day.[548] One of this physicians slide presentations includes information on promoting antipsychotics in children for "conduct disorders."[549]

The Complaint also alleges that AstraZeneca promoted Seroquel heavily to primary care physicians, including instructing sales representatives how to "overcome resistance to prescribing Seroquel to primary care physicians."[550]

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[544] *Id.* ¶¶38-40. The June 2002 newsletter stated: "… it is increasingly clear that Seroquel is the best choice for improving quality of life in elderly patients and offers clear advantages in the Long-term Care setting."
[545] *Id.* ¶ 48-57. One physician was paid $134,000 in 2003. This physician conducted a study of 30 children to treat mania in bipolar adolescents. The same physician's husband received the catering business for the off-label Seroquel lunches. *Id.* ¶ 53. She made numerous presentations for AstraZeneca, for instance, she presented at an Orphanage in Ohio on 2003 for $1,500, encouraging the benefits of Seroquel to treat children at the orphanage. *Id.* ¶ 57.
[546] *Id.* ¶¶ 58.
[547] *Id.* ¶¶ 68-71.
[548] *Id.* ¶¶ 70, 76.
[549] *Id.* ¶ 73.
[550] *Id.* ¶¶ 87-89.

4.1.20 Topamax—Johnson & Johnson (Ortho-McNeill Pharmaceuticals)

Overview

On April 29, 2010, the Department of Justice announced that Johnson & Johnson, through subsidiaries Ortho-McNeill Pharmaceuticals LLC and Ortho-McNeil-Janssen Pharmaceuticals Inc., agreed to pay more than $81 million to resolve criminal and civil liabilities arising from off label promotion of Topamax.[551] Ortho-McNeil Pharmaceutical LLC pled guilty to a misdemeanor and paid a $6.14 million criminal fine for violating the Food, Drug and Cosmetic Act by misbranding Topamax.[552] Ortho-McNeil-Janssen Pharmaceuticals Inc. paid $75.37 million to resolve civil allegations under the False Claims Act for promoting Topamax for unapproved uses.[553] The federal share of the civil settlement is $50,688,483.52 and the state Medicaid share is $24,681,516.48.[554] The whistleblower received more than $9 million of the federal share of the settlement amount.[555] As part of the settlement, Ortho-McNeil-Janssen Pharmaceuticals entered into an "expansive" corporate integrity agreement with the Office of Inspector General.[556]

Ortho-McNeil mounted a national marketing and kickback campaign to promote Topamax for a broad range of off-label uses. The Complaint alleged that Ortho-McNeil

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[551] Press Release, Two Johnson & Johnson Subsidiaries to Pay Over $81 Million to Resolve Allegations of Off-label Promotion of Topamax, Department of Justice (Apr. 29, 2010).
[552] *Id.*
[553] *Id.*
[554] *Id.*
[555] *Id.* at 2.
[556] *Id.* at 2.

promoted Topamax for unapproved uses ranging from weight loss to alcohol dependence, eating disorders, and mood and anxiety disorders.[557]

Clinical

The FDA approved Topamax on October 26, 1996 as adjunctive therapy for the treatment of partial onset seizures or primary tonic-clonic seizures in adults. A list of the indications and off-label uses per drug as published in the AHFS from 1997 through 2010 is available upon request. Since that time, the FDA has approved Topamax in different dosages titration schedules, and as an add-on for pediatric patients with partial onset seizures. Topamax is indicated for use as an adjunctive therapy for adults and pediatric patients ages 2 to 6 years with partial onset seizures or primary generalized tonic-clonic seizures, and in patients 2 years of age and older with seizures associated with Lennox-Gastaut Syndrome.

In 1999, the FDA approved Topamax as an add-on treatment for primary generalized tonic-clonic seizures in adults and pediatric patients. On or about Dec 23, 2002 Ortho-McNeil submitted a supplemental new drug application to the FDA for the approval to market Topamax for the prevention of migraine headaches in adults.

Factual Allegations & Admissions

Former employee, Dr. Gary Spivack, brought the lawsuit against Ortho-McNeil Pharmaceuticals, Inc. and Johnson & Johnson to recover damages and civil penalties on behalf of the United States of America, the States and District of Columbia for violations

[557] Second Amended Complaint United States of America et al ex rel. Dr. Gary R. Spivack v. Johnson & Johnson, and Ortho-McNeil Pharmaceutical Inc., 04-cv-11886 (D. Mass.), ¶ 4

of the Federal Civil FCA.[558] The alleged FCA violations stem from promotion of Topamax for numerous off-label treatments and kickbacks to physicians for prescribing the drug off-label.[559] The off-label uses include: weight loss, alcohol dependency, eating disorders, mood and anxiety disorders, post-traumatic stress syndrome, Tourette's syndrome, essential tremor, and diabetic neuropathic pain.[560]

At least in 2007, and likely longer, Ortho-McNeil staged Consultant Conferences to promote Topamax for off-label uses.[561] Providers who participated in the Conferences were paid $500 to attend[562] the Conferences.

The Complaint alleges that Ortho-McNeil hired hundreds of "consultants" who also were potentially high-prescribing providers for the purposes of marketing Topamax.[563] Some of the uses promoted by Ortho-McNeil were contradicted by previous studies funded by Ortho-McNeil or other subsidiaries of Johnson & Johnson.[564] Other promotion of off-label uses focused on unsubstantiated claims of superiority to other drug products.[565]

The Complaint also alleges that Ortho-McNeil failed to properly disclose serious side effects related to Topamax.[566] For instance, despite the fact that two trials on Topamax in treating obesity were stopped because of a high incidence of side effects,

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[558] United States of America et al. ex rel. Dr. Gary R. Spivack v. Johnson & Johnson, and Ortho-McNeil Pharmaceutical Inc., No. 04-cv-11886, Dec. 7, 2007 (D. Mass.).
[559] *Id.* ¶ 3.
[560] *Id.* ¶ 20.
[561] *Id.* ¶ 57.
[562] *Id.* ¶¶ 64-65.
[563] *Id.* ¶ 66.
[564] *Id.* ¶¶ 70.
[565] *Id.* ¶¶ 75-77.
[566] *Id.* ¶ 85.

Ortho-McNeil promoted Topamax for this use without disclosing the high incidence of side effects.[567]

4.1.21 TOBI–Novartis (Chiron Corp.)

Overview

On May 4, 2010, the Department of Justice announced that Novartis Vaccines & Diagnostics Inc. and Novartis Pharmaceuticals Corp. agreed to pay $72.5 million to resolve civil False Claims Act allegations arising from the off-label promotion of TOBI.[568] Chiron acquired the rights to TOBI on or about August 14, 2000.[569] The United States received $43.5 million for the federal claims, and the states received $29 million.[570] The whistleblowers who brought the original lawsuit received $7.825 million of the federal portion of the settlement.[571] The timeframe alleged for the off-label promotion was January 1, 2001 through July 31, 2006.[572]

Clinical

The FDA approved TOBI on December 22, 1997 for the management of cystic fibrosis ("CF") patients with *Pseudomonas aeruginosa*. A list of the indications and off-label uses per drug as published in the AHFS from 1997 through 2010 is available upon

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[567] *Id*. ¶¶ 84-86.
[568] Press Release, Novartis Vaccines & Diagnostics to Pay More Than $72 million to Resolve False Claims Act Allegations Concerning TOBI, Department of Justice, Office of Public Affairs (May 4, 2010).
[569] United States of America, ex. rel. Robert Lally, Courtney Davis and William Manos v. Novartis Vaccines and Diagnostics, Inc.; and Express Scripts, Inc. (fdba Priority Healthcare Corp.), No. 06-cv-6303, Oct. 6, 2006 (N.D. CA).
[570] *Id*.
[571] *Id*.
[572] *Id*.

request. CF is a genetic disease affecting about 30,000 children and adults in the United States. CF causes the body to produce abnormally thick, sticky mucus that clogs the lungs and obstructs the pancreas. According to the CF Foundation's National Patient Registry, median age of survival for a person with CF is 33.4 years.

Factual Allegations & Admissions

Three former employees of Chiron Corp. brought suit against Novartis Vaccines and Diagnostics, Inc. for alleged violations of the FCA. The specific allegations included promoting TOBI for off-label uses such as: bronchietasis ("BE"), ventilator assisted pneumonia ("VAP"), as a first-line treatment for children not chronically infected with P. aeruginosa, and/or with lung function greater than 75%, and for those below the age of six.[573] Training to sales representatives included providing them with studies about off-label uses of TOBI "which the sales representatives were told to destroy or return to Chiron after review;" scripted inquiries where the sales representatives were coached to engage physicians in off-label discussions; and presentations to coach the sales representatives in how to guide the off-label discussions with physicians.[574] The Complaint also alleges that Chiron provided sales representatives with a special database to track off-label sales and activities, which Chiron's sales operations unit and marketing department managed.[575]

Chiron required sales persons to spend 10% to 30% of their time calling on physicians in off-label areas, and provided monetary incentives to sales representatives to

[573] *Id*. ¶ 27.
[574] *Id*. ¶ 34(d).
[575] *Id*. ¶ 34(e).

participate in off-label promotion.[576] Chiron instructed its sales people to tell doctors that TOBI reduces hospital stays and reduces exacerbations in patients hospitalized for respiratory problems, and that TOBI has studies in CF and demonstrated a successful track record, among other things, but did not instruct sales representatives to qualify that as being in connection with the management of a specific type of bacterial infection (P. aeruginosa).[577] These are just a few examples of off-label promotional tactics among many listed within the Complaint.[578]

4.2 The Vioxx® and Zocor®

The Vioxx® and Zocor® lawsuit demonstrates another scheme that falls under the auspices of the False Claims Act. The allegations involved a pricing scheme. On February 7th, 2008, Merck & Co, Inc. agreed to pay more than $650 million to settle charges of overbilling the government for rofecoxib (Vioxx®) and simvastatin (Zocor®), "cheating Medicaid out of millions of dollars in discounts over eight years."[579] The pricing scheme employed by Merck utilized nominal pricing for hospitals so that they could give substantial discounts to the hospitals[580] to induce prescribing of the two drugs.

[576] *Id*. ¶ 34(j-k).
[577] *Id*. ¶ 34(n).
[578] *Id*. ¶¶ 34-36.
[579] Merck to Pay more than $650 million to resolve claims of fraudulent price reporting and kickbacks, Department of Justice, February 7th, 2008, http://www.usdoj.gov/opa/pr/2008/February/08_civ_094.html.
[580] Discounts of more than 90% the AMP were given to hospitals and excluded from Best Price reporting (required for Medicaid reimbursement of the agent). The Medicaid Rebate Act and "Best Price" Provision, Taxpayers Against Fraud, http://www.drugfraudsettlement.com/Medicaid-and-States/Best-Price (Available at Taf.org accessed 7/19/2008).

The goal of the pricing scheme was to have patients initiate therapy on the two medications while in the hospital so that they would continue taking the agents when they left the hospital (the spillover effect).[581] After leaving the hospital, the Medicaid patient would bring their prescription to their outpatient pharmacy and the government would then reimburse Merck a much higher price than the one that Merck offered the hospitals.

The Medicaid Rebate Program requires that drug companies report their best price (BP) and average manufacturer price (AMP) to Medicaid. CMS then calculates reimbursement amounts based on the BP and AMP reported by the drug company. The Merck pricing scheme did not report the hospital discount structure to Medicaid as the best price.[582] Merck did not admit any wrongdoing with the pricing scheme, but still agreed to settle the charges.

The pricing scheme and allegations of illegal kickbacks to physicians for prescribing the two agents led to government overpayments. This case presents a general example of another type of fraudulent scheme employed by some companies.

Summary of Qualitative Findings

The following paragraphs summarize some of the qualitative findings not used as variables in the quantitative portion of this study. Of the 21 settled cases, all but one involved allegations of off-label promotion. One case only involved allegations of kickbacks (in exchange for prescribing the drug Cardizem LA) and seven of the cases involved allegations of off-label promotion and kickbacks. There were 16 total therapeutic classes represented by the sample with three drugs each from the

[581] *Id.*
[582] *Id.*

antipsychotics, growth hormone/anabolic hormones, seizure disorders, and two drugs each from the antineoplastics, immunologics, selective serotonin reuptake inhibitors, and ten drugs each from a different therapeutic class. About 80% of the cases are settled two or more years after the Complaint date. About 40% of the cases were filed in the District of Massachusetts (8 of 21). The number of settled cases involving marketing schemes is increasing. In 2004, there was one settlement and then two in 2005 and 2006. In 2007, eight cases settled and then three in 2009 and four as of mid-2010.

Tables B-1 and **B-2** describe information collected from the case studies. **Table B-1** lists the company, year of settlement, total settlement amount, drug(s) involved, date of the Complaint, and U.S. District Court where the Complaint was filed. **Table B-2** lists the therapeutic class for each drug.

Quantitative study results

The results of data analysis are presented in three sections. The first section presents the descriptive statistics for each continuous variable and the dependent variable (total settlement amount). The second section presents results of statistical analysis using the Chi-square test regarding the associations and trends between the independent variables and the total settlement amount. The third section presents results of statistical analysis using the Mantel-Haenszel Chi-square test based on the results obtained from the traditional Chi-square tests to further assess associations and trends between certain independent variables and the total settlement amount.

I. Descriptive Statistics

Table F presents the mean, standard deviation, and range for all continuous variables. **Table G** presents the means for each variable as categorized for purposes of the Chi-square and Mantel-Haenszel statistical analysis. **Tables C, D, H, I, J, and K** display the amounts per variable for each drug. The drug resulting in the highest and lowest amounts per variable are discussed in more detail below.

Total Settlement Amount

Both the highest and lowest settlement amounts involved drugs discontinued from the market due to safety concerns. The lowest settlement amount was 8,000,000 represented by the amount collected from Bayer Pharmaceuticals for its involvement with illegally promoting the drug Baycol as having comparable efficacy to Lipitor, another statin, and encouraging patients to start at a higher dose of Baycol than its recommended initial dosing.[583] Bayer withdrew Baycol from the market in August 2001 after postmarketing studies showed potentially severe adverse effects, especially concerning myopathy. Baycol was used to treat primary hypercholesterolemia and mixed dyslipidemia.

The largest settlement amount was $1,802,524,316 Billion associated with the off-label promotion of Bextra. The government settled with Pfizer for the following allegations: paying kickbacks for nine drugs, Aricept, Celebrex, Lipitor, Norvasc, Relpax,

[583] Amended Complaint, United States of America et al. ex rel. Laurie Simpson v. Bayer Healthcare d/b/a Bayer Healthcare Pharmaceuticals; Bayer Pharmaceuticals Corp.; Bayer Corp.; and Bayer A.G., No. 06-cv-4796, Mar. 31, 2008 (D. N.J.).

Viagra, Zithromax, Zoloft, and Zyrtec (Kickback Drugs);[584] off-label promotion for Geodon ($301,462,065), Zyvox ($97,945,019), and Lyrica ($48,223,886); civil liability for Bextra ($502,524,316) and a criminal fine for Bextra ($1.3 billion). Bextra was also withdrawn from the U.S. market on April 7, 2005 because the overall risk versus benefit profile of Bextra was unfavorable. [585] Bextra was used for the relief of the signs and symptoms of osteoarthritis and adult rheumatoid arthritis and for the treatment of primary dysmenorrheal. **Table H** shows the adjusted settlement amounts for each drug.

Total IMS units

The lowest IMS units were 1,689,191 for Actimmune, sold by Intermune, Inc. The FDA initially approved Actimmune to reduce the frequency and severity of serious infections in adults and children 1 year of age or older with chronic granulomatous disease and to delay the time to disease progression in adults and children with severe, malignant osteopetrosis. The highest IMS units were 9,729,710,751 for Neurontin sold by Pfizer (Warner-Lambert, Park-Davis). The FDA initially approved Neurontin as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults with epilepsy. **Table H** shows the total IMS units for each drug.

Total IMS dollars

[584] Pfizer Fact Sheet: Pfizer to pay $2.3 billion to resolve criminal and civil health care liability relating to fraudulent marketing and the payment of kickbacks, STOPMedicareFraud.gov, U.S. Department of Health and Human Services and U.S. Department of Justice, available at STOPMedicareFRAUD.gov (last visited Sept. 28, 2010).

[585] FDA Alert: Information for Healthcare Professionals: valdecoxib (marketed as Bextra), dated April 7, 2005, available at www.fda.gov (last visited Aug. 22, 2012).

The lowest total dollar amount was $128,373,386 for Trisenox sold by Cell Therapeutics, Inc. (CTI). The FDA initially approved Trisenox for treatment of 20 to 30% of APL patients who have relapsed from standard therapies (retinoid and anthracycline chemotherapy). The highest total dollar amount was $ 25,902,098,356 for Zyprexa, sold by Eli Lilly & Co. The FDA initially approved Zyprexa for the treatment of manifestations of psychotic disorders. **Table H** shows the total IMS dollar amounts for each drug.

Total Medicaid units

The lowest total Medicaid units were 32,574 for Trisenox. The highest Medicaid units were 2,097,393,979 for Seroquel sold by Astra Zeneca. The FDA initially approved Seroquel for treatment of manifestations of psychotic disorders. **Table H** shows the total Medicaid units for each drug.

Total Medicaid dollars

The drugs with the highest and lowest Medicaid dollar amounts were the same as the drugs with the highest and lowest IMS dollars. The lowest Medicaid dollars were $723,354 for Actimmune. The highest Medicaid total dollar amount was $12,534,138,238 for Zyprexa sold by Eli Lilly & Co. **Table H** shows the total Medicaid dollar amounts for each drug.

Estimated Medicaid units allocated to off-label use

The lowest estimated Medicaid units allocated to off-label use were 15,993 for Trisenox. The highest Medicaid units allocated to off-label use were 1,878,293,755 for

Neurontin. **Table K** shows the estimated Medicaid units allocated to off-label use for each drug.

Estimated Medicaid dollars allocated to off-label use

The lowest estimated Medicaid dollars allocated to off-label use was $355,139 for Trisenox. The highest Medicaid dollars allocated to off-label use was 1,878,293,755 for Neurontin. **Table K** shows the Medicaid dollars allocated to off-label use for each drug.

Estimated Medicaid units allocated to non-evidence based uses

The lowest estimated Medicaid units allocated to non-evidence based use were 2,270 for Trisenox. The highest Medicaid units allocated to non-evidence based use were 1,762,798,088 for Neurontin. **Table K** shows the Medicaid units allocated to non-evidence based use for each drug.

Estimated Medicaid dollars allocated to non-evidence based uses

The lowest estimated Medicaid dollars allocated to non-evidence based use was $50,424 for Trisenox. The highest Medicaid dollars allocated to non-evidence based use was $4,044,972,839 for Zyprexa. **Table K** shows the Medicaid dollars allocated to non-evidence based use for each drug.

Estimated IMS units allocated to off-label use

The lowest estimated IMS units allocated to off-label use were 994,266 for Serostim sold by Serono, Inc. The FDA initially approved Serostim for treatment of AIDS wasting in HIV-infected patients. The highest IMS units allocated to off-label use were 9,609,514,391 for Neurontin. **Table J** shows the total IMS units allocated to off-label use for each drug.

Estimated IMS dollars allocated to off-label use

The lowest estimated IMS dollars allocated to off-label use were $34,202,043 for Baycol. The highest IMS dollars allocated to off-label use were $20,090,829,633 for Zyprexa. **Table J** shows the total IMS dollars allocated to off-label use for each drug.

Estimated IMS dollars allocated to non-evidence based uses

The lowest IMS dollars allocated to non-evidence based were $8,948,658 for Trisenox. The highest IMS dollars allocated to non-evidence based use were $10,812,329,122 for Seroquel. **Table J** shows the total IMS dollars allocated to non-evidence based use for each drug.

Estimated IMS units allocated to non-evidence based uses

The lowest estimated IMS units allocated to non-evidence based use were 287,364 for Trisenox. The highest IMS units allocated to non-evidence based use were 9,018,628,503 for Neurontin. **Table J** shows the total IMS units allocated to non-evidence based use for each drug.

Total Promotional Dollars

The lowest amount spent on promotion was $1,125,178 for Actimmune. The highest amount spent on promotion was $3,171,773,141 for Lexapro, sold by Forest Labs. The FDA initially approved Lexapro for treatment of major depressive disorder. **Table I** shows the dollars spent on promotion of each drug.

Estimated Promotional Dollars allocated to off-label uses

The lowest estimated amount spent on promotion related to off-label use was $861,005 for Genotropin, sold by Pfizer (Pharmacia and Upjohn Co.). The FDA initially

approved Genotropin for treatment of pediatric patients who have growth failure due to an inadequate secretion of endogenous growth hormone. The highest amount spent on promotion related to off-label use was $2,458,214,152 for Lexapro. **Table I** shows the dollars spent on promotion of each drug related to off-label use.

Estimated Promotional Dollars allocated to non-evidence based uses

The lowest amount spent on promotion allocated to non-evidence based use was $137,145 for Trisenox. The highest spent on promotion allocated to non-evidence based use was $987,109,942 for Lexapro. **Table I** shows the dollars spent on promotion of each drug allocated to non-evidence based use.

Off-label use relative to all uses

The lowest ratio of off-label use relative to all uses was 0.05 for Baycol. The highest ratio of off-label use relative to all uses was 1 for Actimmune where all uses reported were for an off-label use. **Table C** shows the ratio of off-label use relative to all uses.

Non-evidence based use relative to all uses

The lowest ratio of non-evidence based use relative to all uses was 0.04 for Baycol. The highest ratio of non-evidence based use relative to all uses was 1 for Actimmune where all uses reported were for a non-evidence based use. **Table D** shows the ratio of non-evidence based use relative to all uses.

II. Chi-square tests

As discussed in more detail below, the Chi-square tests did not show a statistical significant association between any of the nominal variables and total settlement amount. Most of the associations tested between the continuous independent variables and total settlement amount showed the lack of a statistically significant association. However, a significant association did exist between the following independent variables and total settlement amount: estimated dollars spent through Medicaid allocated to non-evidence based use ("MedDolClin" with a p-value of 0.0405); total estimated utilization (measured in units) allocated to non-evidence based use ("UnitClin" with a p-value of 0.0191); total estimated utilization (measured in units) allocated to off-label use ("UnitOff" with a p-value of 0.0464). **Table F** shows the p-values for all variables tested. The contingency tables for each statistically significant test result showed a trend toward a positive association in that as the independent variable increased, the total settlement amount also increased (i.e., when total units allocated to off-label use increased, the total settlement amount increased with the counterfactual also true).

The following variables had a p-value>0.05 but less than 0.1: estimated total Medicaid utilization (measured in units) allocated to non-evidence based use ("MedUnitClin" with a p-value of 0.0932); estimated total IMS dollars allocated to non-evidence based use ("TotDolClin" with a p-value of 0.0619); Medicaid utilization (measured in units) allocated to off-label use ("MedUnitOff" with a p-value of 0.0932). The contingency tables for each test with a p-value below 0.1 also tended towards a positive association. The following pages show the hypothesis and results of the Chi-

square tests including p-values and contingency tables for all tested variables. **Table F** shows the p-value from the Chi-square test of association between each variable and total settlement amount.

Hypothesis A:

A greater proportion of drugs with labels that included a black box warning will result in a higher settlement than those drugs without such a warning.

Table of BBstatus by AdjTotSettle			
BBstatus	**AdjTotSettle**		
Frequency **Expected** **Percent** **Row Pct** **Col Pct**	**Under 100 million**	**100+ million**	**Total**
No	7 5.9583 29.17 53.85 63.64	6 7.0417 25.00 46.15 46.15	13 54.17
yes	4 5.0417 16.67 36.36 36.36	7 5.9583 29.17 63.64 53.85	11 45.83
Total	11 45.83	13 54.17	24 100.00
Frequency Missing = 1			

Statistic	DF	Value	Prob
Chi-Square	1	0.7335	0.3917

Explanation:

The p-value of 0.3917 is greater than the significance level of 0.05; therefore, the null hypothesis is accepted. This result indicates that there is not a statistically significant association between Black Box Warning status and the adjusted total settlement amount.

Hypothesis B:

A greater proportion of drugs with labels that included a black box warning relating to at least one of the off-label indications that the government alleged the drug company improperly promoted will result in a higher settlement amount.

Table of BBpromo by AdjTotSettle			
BBpromo	**AdjTotSettle**		
Frequency Expected Percent Row Pct Col Pct	**Under 100 million**	**100+ million**	**Total**
no	9 7.3333 37.50 56.25 81.82	7 8.6667 29.17 43.75 53.85	16 66.67
yes	2 3.6667 8.33 25.00 18.18	6 4.3333 25.00 75.00 46.15	8 33.33
Total	11 45.83	13 54.17	24 100.00
Frequency Missing = 1			

Statistic	DF	Value	Prob
Chi-Square	1	2.0979	0.1475

Fisher's Exact Test	
Cell (1,1) Frequency (F)	9
Left-sided Pr <= F	0.9726
Right-sided Pr >= F	0.1557
Table Probability (P)	0.1283
Two-sided Pr <= P	0.2108

Explanation:

The Chi-square p-value of 0.1475 and Fischer exact p-value of 0.1283 are greater than the significance level of 0.05; therefore, the null hypothesis is accepted. This result indicates that there is not a statistically significant association between whether the Black Box Warning was for a use the government alleged the drug company promoted off-label and the adjusted total settlement amount.

Hypothesis C:

A greater proportion of drugs with at least one FDA warning will result in a higher settlement than those drugs without such a warning.

Table of Warning by AdjTotSettle			
Warning	**AdjTotSettle**		
Frequency Expected Percent Row Pct Col Pct	**Under 100 million**	**100+ million**	**Total**
no	6 5.0417 25.00 54.55 54.55	5 5.9583 20.83 45.45 38.46	11 45.83
yes	5 5.9583 20.83 38.46 45.45	8 7.0417 33.33 61.54 61.54	13 54.17
Total	11 45.83	13 54.17	24 100.00
Frequency Missing = 1			

Statistic	DF	Value	Prob
Chi-Square	1	0.6209	0.4307

Explanation:

The p-value of 0.4307 is greater than the significance level of 0.05; therefore, the null hypothesis is accepted. This indicates that there is not a statistically significant association between FDA issued Warning letters and the adjusted total settlement amount.

Hypothesis D:

A greater proportion of drugs with a greater number of indications will result in a higher settlement amount than those drug with a lower number of FDA-approved indications.

Table of Indications by AdjTotSettle			
Indications	**AdjTotSettle**		
Frequency Expected Percent Row Pct Col Pct	**Under 100 million**	**100+ million**	**Total**
1	3 3.6667 12.50 37.50 27.27	5 4.3333 20.83 62.50 38.46	8 33.33
2-3	4 4.5833 16.67 40.00 36.36	6 5.4167 25.00 60.00 46.15	10 41.67
4+	4 2.75 16.67 66.67 36.36	2 3.25 8.33 33.33 15.38	6 25.00
Total	11 45.83	13 54.17	24 100.00
Frequency Missing = 1			

Statistic	DF	Value	Prob
Chi-Square	2	1.4098	0.4942

Fisher's Exact Test	
Table Probability (P)	0.0707
Pr <= P	0.6631

Explanation:

The Chi-square p-value of 0.4942 and the Fischer's exact p-value is 0.0707 are greater than the significance level of 0.05; therefore, the null hypothesis is accepted. This indicates that there is not a statistically significant association between the number of indications and the adjusted total settlement amount.

Hypothesis E:

A greater proportion of drugs with high amounts spent on promotion will result in higher settlement amounts than those drugs where smaller amounts are spent on promotion.

Table of PromoDollars by AdjTotSettle			
PromoDollars	**AdjTotSettle**		
Frequency **Expected** **Percent** **Row Pct** **Col Pct**	**Under 100 million**	**100+ million**	**Total**
Under 50 million	7 5.9583 29.17 53.85 63.64	6 7.0417 25.00 46.15 46.15	13 54.17
50+ million	4 5.0417 16.67 36.36 36.36	7 5.9583 29.17 63.64 53.85	11 45.83
Total	11 45.83	13 54.17	24 100.00
Frequency Missing = 1			

Statistic	DF	Value	Prob
Chi-Square	1	0.7335	0.3917

Explanation:

The p-value of 0.3917 is greater than the significance level of 0.05; therefore, the null hypothesis is accepted. This indicates that there is not a statistically significant association between the total promotional spend on each drug and the adjusted total settlement amount.

Hypothesis F:

As the overall number of units (i.e., tablets, capsules) sold of each drug increases, the settlement amount increases.

Table of Units by AdjTotSettle			
Units	**AdjTotSettle**		
Frequency **Expected** **Percent** **Row Pct** **Col Pct**	**Under 100 million**	**100+ million**	**Total**
Under 500 million	5 4.3478 21.74 50.00 50.00	5 5.6522 21.74 50.00 38.46	10 43.48
500+ million	5 5.6522 21.74 38.46 50.00	8 7.3478 34.78 61.54 61.54	13 56.52
Total	10 43.48	13 56.52	23 100.00
Frequency Missing = 1			

Statistic	DF	Value	Prob
Chi-Square	1	0.3062	0.5800

Fisher's Exact Test	
Cell (1,1) Frequency (F)	5
Left-sided Pr <= F	0.8356
Right-sided Pr >= F	0.4479
Table Probability (P)	0.2835
Two-sided Pr <= P	0.6850

Explanation:

The Chi-square p-value of 0.5800 and Fischer's Exact p-value of 0.2835 are greater than the significance level of 0.05; therefore, the null hypothesis is accepted. This indicates that there is not a statistically significant association between the total IMS units of each drug and the adjusted total settlement amount.

Hypothesis G:

As the number of Medicaid units (i.e., tablets, capsules) sold of each drug increases, the settlement amount increases.

Table of medUnit by AdjTotSettle			
medUnit	**AdjTotSettle**		
Frequency **Expected** **Percent** **Row Pct** **Col Pct**	**Under 100 million**	**100+ million**	**Total**
Under 100 million	8 6.4167 33.33 57.14 72.73	6 7.5833 25.00 42.86 46.15	14 58.33
100+ million	3 4.5833 12.50 30.00 27.27	7 5.4167 29.17 70.00 53.85	10 41.67
Total	11 45.83	13 54.17	24 100.00

Statistic	DF	Value	Prob
Chi-Square	1	1.7311	0.1883

Fisher's Exact Test	
Cell (1,1) Frequency (F)	8
Left-sided Pr <= F	0.9598
Right-sided Pr >= F	0.1846
Table Probability (P)	0.1444
Two-sided Pr <= P	0.2397

Explanation:

The Chi-square p-value of 0.1883 and Fischer's exact p-value of 0.1444 are greater than the significance level of 0.05; therefore, the null hypothesis is accepted. This indicates that there is not a statistically significant association between the total Medicaid units of each drug and the adjusted total settlement amount.

Hypothesis H:

As the overall sales dollars for each drug increases, the settlement amount increases.

Table of TotalDollars by AdjTotSettle			
TotalDollars	**AdjTotSettle**		
Frequency **Expected** **Percent** **Row Pct** **Col Pct**	**Under 100 million**	**100+ million**	**Total**
Under 1.5 billion	6 4.3478 26.09 60.00 60.00	4 5.6522 17.39 40.00 30.77	10 43.48
1.5 billion	4 5.6522 17.39 30.77 40.00	9 7.3478 39.13 69.23 69.23	13 56.52
Total	10 43.48	13 56.52	23 100.00

Statistic	DF	Value	Prob
Chi-Square	1	1.9652	0.1610

Fisher's Exact Test	
Cell (1,1) Frequency (F)	6
Left-sided Pr <= F	0.9668
Right-sided Pr >= F	0.1644
Table Probability (P)	0.1312
Two-sided Pr <= P	0.2215

Explanation:

The Chi-square p-value of 0.1610 and Fischer's Exact p-value of 0.1312 are greater than the significance level of 0.05; therefore, the null hypothesis is accepted. This indicates that there is not a statistically significant association between the total IMS dollars of each drug and the adjusted total settlement amount.

Hypothesis I:

As the amount of sales dollars spent through Medicaid increases for each drug, the settlement amount increases.

Table of medDol by AdjTotSettle			
medDol	**AdjTotSettle**		
Frequency Expected Percent Row Pct Col Pct	**Under 100 million**	**100+ million**	**Total**
Under 500 million	8 6.4167 33.33 57.14 72.73	6 7.5833 25.00 42.86 46.15	14 58.33
500+ million	3 4.5833 12.50 30.00 27.27	7 5.4167 29.17 70.00 53.85	10 41.67
Total	11 45.83	13 54.17	24 100.00

Statistic	DF	Value	Prob
Chi-Square	1	1.7311	0.1883

Fisher's Exact Test	
Cell (1,1) Frequency (F)	8
Left-sided Pr <= F	0.9598
Right-sided Pr >= F	0.1846
Table Probability (P)	0.1444
Two-sided Pr <= P	0.2397

Explanation:

The Chi-square p-value of 0.1883 and Fischer's Exact p-value of 0.1444 are greater than the significance level of 0.05; therefore, the null hypothesis is accepted. This indicates that there is not a statistically significant association between the total Medicaid dollars of each drug and the adjusted total settlement amount.

Hypothesis J:

As the off-label prescribing relative to total uses for each drug increases, the settlement amount increases.

Table of NdtiOffRegRate by AdjTotSettle			
NdtiOffRegRate	**AdjTotSettle**		
Frequency Expected Percent Row Pct Col Pct	**Under 100 million**	**100+ million**	**Total**
less than .06	1 0.4583 4.17 100.00 9.09	0 0.5417 0.00 0.00 0.00	1 4.17
.06 or greater	10 10.542 41.67 43.48 90.91	13 12.458 54.17 56.52 100.00	23 95.83
Total	11 45.83	13 54.17	24 100.00
Frequency Missing = 1			

Statistic	DF	Value	Prob
Chi-Square	1	1.2332	0.2668

Fisher's Exact Test	
Cell (1,1) Frequency (F)	1
Left-sided Pr <= F	1.0000
Right-sided Pr >= F	0.4583
Table Probability (P)	0.4583
Two-sided Pr <= P	0.4583

Explanation:

The Chi-square p-value of 0.2668 and Fischer's Exact p-value of 0.4583 are greater than the significance level of 0.05; therefore, the null hypothesis is accepted. This indicates that there is not a statistically significant association between off-label prescribing relative to total uses for each drug and the adjusted total settlement amount.

Hypothesis K:

As the prescribing for non-evidence based uses relative to total uses for each drug increases, the settlement amount increases.

Table of NdtiNonClinicalRate by AdjTotSettle			
NdtiNonClinicalRate	**AdjTotSettle**		
Frequency **Expected** **Percent** **Row Pct** **Col Pct**	**Under 100 million**	**100+ million**	**Total**
less than .39	7 5.9583 29.17 53.85 63.64	6 7.0417 25.00 46.15 46.15	13 54.17
.39 or greater	4 5.0417 16.67 36.36 36.36	7 5.9583 29.17 63.64 53.85	11 45.83
Total	11 45.83	13 54.17	24 100.00
Frequency Missing = 1			

Statistic	DF	Value	Prob
Chi-Square	1	0.7335	0.3917

Explanation:

The p-value of 0.3917 is greater than the significance level of 0.05; therefore, the null hypothesis is accepted. This indicates that there is not a statistically significant association between the prescribing for non-evidence based uses relative to total uses for each drug and the adjusted total settlement amount.

Hypothesis L:

As the total estimated promotional dollars allocated to non-evidence based use increases, the settlement amount increases.

Table of PromoDolClin by AdjTotSettle			
PromoDolClin	**AdjTotSettle**		
Frequency **Expected** **Percent** **Row Pct** **Col Pct**	**Under 100 million**	**100+ million**	**Total**
< 100 million	8 6.875 33.33 53.33 72.73	7 8.125 29.17 46.67 53.85	15 62.50
100 million plus	3 4.125 12.50 33.33 27.27	6 4.875 25.00 66.67 46.15	9 37.50
Total	11 45.83	13 54.17	24 100.00

Statistic	DF	Value	Prob
Chi-Square	1	0.9063	0.3411

Fisher's Exact Test	
Cell (1,1) Frequency (F)	8
Left-sided Pr <= F	0.9164
Right-sided Pr >= F	0.3001
Table Probability (P)	0.2166
Two-sided Pr <= P	0.4225

Explanation:

The Chi-square p-value of 0.3411 and Fischer's Exact p-value of 0.2166 are greater than the significance level of 0.05; therefore, the null hypothesis is accepted. This indicates that there is not a statistically significant association between the estimated promotional dollars spent on each drug allocated to non-evidence based use and the adjusted total settlement amount.

Hypothesis M:

As the total estimated promotional dollars allocated to off-label use increases, the settlement amount increases.

Table of PromoDolOff by AdjTotSettle			
PromoDolOff	**AdjTotSettle**		
Frequency **Expected** **Percent** **Row Pct** **Col Pct**	**Under 100 million**	**100+ million**	**Total**
< 50 million	8 6.4167 33.33 57.14 72.73	6 7.5833 25.00 42.86 46.15	14 58.33
50 million plus	3 4.5833 12.50 30.00 27.27	7 5.4167 29.17 70.00 53.85	10 41.67
Total	11 45.83	13 54.17	24 100.00

Statistic	DF	Value	Prob
Chi-Square	1	1.7311	0.1883

Fisher's Exact Test	
Cell (1,1) Frequency (F)	8
Left-sided Pr <= F	0.9598
Right-sided Pr >= F	0.1846
Table Probability (P)	0.1444
Two-sided Pr <= P	0.2397

Explanation:

The Chi-square p-value of 0.1883 and Fischer's Exact p-value of 0.1444 are greater than the significance level of 0.05; therefore, the null hypothesis is accepted. This indicates that there is not a statistically significant association between the estimated promotional dollars spent on each drug allocated to off-label uses and the adjusted total settlement amount.

Hypothesis N:

As the total estimated Medicaid utilization (measured in units) allocated to non-evidence based use increases, the settlement amount increases.

Table of MedUnitClin by AdjTotSettle			
MedUnitClin	**AdjTotSettle**		
Frequency **Expected** **Percent** **Row Pct** **Col Pct**	**Under 100 million**	**100+ million**	**Total**
< 50 million	8 5.9583 33.33 61.54 72.73	5 7.0417 20.83 38.46 38.46	13 54.17
50 million plus	3 5.0417 12.50 27.27 27.27	8 5.9583 33.33 72.73 61.54	11 45.83
Total	11 45.83	13 54.17	24 100.00

Statistic	DF	Value	Prob
Chi-Square	1	2.8179	0.0932

Explanation:

The p-value of 0.0932 is greater than the significance level of 0.05; therefore, the null hypothesis is accepted. This indicates that there is not a statistically significant association between the total estimated Medicaid utilization (measured in units) allocated to non-evidence based use and the settlement amount. Although the association did not reach the level of significance assigned to this study, the contingency table shows a trend

toward a positive association. The expected number of values having a greater settlement amount and greater number of Medicaid units allocated to non-evidence based use was 5.9583, but the actual results were higher. A similar result is shown in the direction of lower settlement and subsequent lower number of estimated Medicaid units allocated to non-evidence based use.

Hypothesis O:

As the total estimated utilization (measured in units) allocated to non-evidence based use increases, the settlement amount increases.

Table of UnitClin by AdjTotSettle			
UnitClin	**AdjTotSettle**		
Frequency Expected Percent Row Pct Col Pct	**Under 100 million**	**100+ million**	**Total**
< 200 million	8 5.2174 34.78 66.67 80.00	4 6.7826 17.39 33.33 30.77	12 52.17
200 million plus	2 4.7826 8.70 18.18 20.00	9 6.2174 39.13 81.82 69.23	11 47.83
Total	10 43.48	13 56.52	23 100.00

Statistic	DF	Value	Prob
Chi-Square	1	5.4900	0.0191

Fisher's Exact Test	
Cell (1,1) Frequency (F)	8
Left-sided Pr <= F	0.9978
Right-sided Pr >= F	0.0260
Table Probability (P)	0.0238
Two-sided Pr <= P	0.0361

Explanation:

The Chi-square p-value of 0.0191 and Fischer's Exact p-value of 0.0238 are less than the significance level of 0.05; therefore, the null hypothesis is rejected. This indicates that there is a statistically significant association between total estimated utilization allocated to non-evidence based use and the settlement amount. Examination of the cells of the contingency table indicates that the association is in the direction hypothesized. The drugs with the highest units allocated to non-evidence based use tended to generate higher settlement amounts than those with lower units allocated to non-evidence based use. The contingency table also demonstrates that the counterfactual is true. The drugs with the lowest units allocated to non-evidence based use tended to generate lower settlement amounts than those with lower units allocated to non-evidence based use.

Hypothesis P:

As the estimated dollars spent through Medicaid allocated to non-evidence based use increases, the settlement amount increases.

Table of MedDolCLin by AdjTotSettle			
MedDolCLin	**AdjTotSettle**		
Frequency Expected Percent Row Pct Col Pct	**Under 100 million**	**100+ million**	**Total**
< 140 million	8 5.5 33.33 66.67 72.73	4 6.5 16.67 33.33 30.77	12 50.00
140 million+	3 5.5 12.50 25.00 27.27	9 6.5 37.50 75.00 69.23	12 50.00
Total	11 45.83	13 54.17	24 100.00

Statistic	DF	Value	Prob
Chi-Square	1	4.1958	0.0405

Explanation:

The Chi-square p-value of 0.0405 is less than the significance level of 0.05; therefore, the null hypothesis is rejected. This indicates that there is a statistically significant association between estimated dollars spent through Medicaid allocated to non-evidence based use and the settlement amount. Examination of the cells of the contingency table indicate that the association is in the direction hypothesized. The drugs

with the highest Medicaid dollars allocated to non-evidence based use tended to generate higher settlement amounts than those with a lower Medicaid dollars allocated to non-evidence based use. The contingency table also demonstrates that the counterfactual is true. The drugs with the lowest Medicaid dollars allocated to non-evidence based use tended to generate lower settlement amounts than those with lower Medicaid dollars allocated to non-evidence based use.

Hypothesis Q:

As the estimated amount of overall dollars used for non-evidence based use increases, the settlement amount increases.

Table of TotDolClin by AdjTotSettle			
TotDolClin	**AdjTotSettle**		
Frequency Expected Percent Row Pct Col Pct	**Under 100 million**	**100+ million**	**Total**
< 1 billion	7 4.7826 30.43 63.64 70.00	4 6.2174 17.39 36.36 30.77	11 47.83
1 billion+	3 5.2174 13.04 25.00 30.00	9 6.7826 39.13 75.00 69.23	12 52.17
Total	10 43.48	13 56.52	23 100.00

Statistic	DF	Value	Prob
Chi-Square	1	3.4862	0.0619

Fisher's Exact Test	
Cell (1,1) Frequency (F)	7
Left-sided Pr <= F	0.9899
Right-sided Pr >= F	0.0736
Table Probability (P)	0.0635
Two-sided Pr <= P	0.0995

Explanation:

The Chi-square p-value of 0.0619 and Fischer's Exact p-value of 0.0635 are greater than the significance level of 0.05; therefore, the null hypothesis is accepted. This indicates that there is not a statistically significant association between estimated IMS dollars allocated to non-evidence based use and the settlement amount. However, the contingency table indicates a trend where the drugs with the highest settlement amounts tended to also have the highest estimated IMS dollars allocated to non-evidence based use. With a p-value so close to 0.05 and the contingency table allocations, it is possible that a larger sample size would allow for a statistically significant result. In which case, it appears there may be a positive association between estimated IMS dollars allocated to non-evidence based use and settlement amount.

Hypothesis R:

As the total Medicaid utilization (measured in units) allocated to off-label use increases, the settlement amount increases.

Table of MedUnitOff by AdjTotSettle			
MedUnitOff	**AdjTotSettle**		
Frequency **Expected** **Percent** **Row Pct** **Col Pct**	**Under 100 million**	**100+ million**	**Total**
< 35 million	8 5.9583 33.33 61.54 72.73	5 7.0417 20.83 38.46 38.46	13 54.17
35 million plus	3 5.0417 12.50 27.27 27.27	8 5.9583 33.33 72.73 61.54	11 45.83
Total	11 45.83	13 54.17	24 100.00

Statistic	DF	Value	Prob
Chi-Square	1	2.8179	0.0932

Explanation:

The p-value of 0.0932 is greater than the significance level of 0.05; therefore, the null hypothesis is accepted. This indicates that there is not a statistically significant association between the total estimated Medicaid units allocated to off-label use and the settlement amount. Examination of the contingency table shows a trend toward a positive

association. The drugs with the highest settlement amount also had the highest number of units allocated to off-label use.

Hypothesis S:

As the total estimated utilization (measured in units) allocated to off-label use increases, the settlement amount increases.

Table of UnitOff by AdjTotSettle			
UnitOff	**AdjTotSettle**		
Frequency Expected Percent Row Pct Col Pct	**Under 100 million**	**100+ million**	**Total**
< 400 million	8 5.6522 34.78 61.54 80.00	5 7.3478 21.74 38.46 38.46	13 56.52
400 million plus	2 4.3478 8.70 20.00 20.00	8 5.6522 34.78 80.00 61.54	10 43.48
Total	10 43.48	13 56.52	23 100.00

Statistic	DF	Value	Prob
Chi-Square	1	3.9685	0.0464

Fisher's Exact Test	
Cell (1,1) Frequency (F)	8
Left-sided Pr <= F	0.9935
Right-sided Pr >= F	0.0571
Table Probability (P)	0.0506
Two-sided Pr <= P	0.0903

Explanation:

The Chi-square p-value of 0.0464 and Fischer's Exact p-value of 0.0506 are less than the significance level of 0.05; therefore, the null hypothesis is rejected. This suggests that there is a statistically significant association between total estimated IMS units allocated to off-label use and the settlement amount. Examination of the cells of the contingency table indicates that the association is in the direction hypothesized. The drugs with the highest units allocated to off-label use tended to generate higher settlement amounts than those with a lower units allocated to off-label use. The contingency table also demonstrates that the counterfactual is true. The drugs with the lowest units allocated to off-label use tended to generate lower settlement amounts than those with higher units allocated to off-label use.

Hypothesis T:

As the estimated amount of dollars spent through Medicaid allocated to off-label use increases, the settlement amount increases.

Table of MedDolOff by AdjTotSettle			
MedDolOff	**AdjTotSettle**		
Frequency **Expected** **Percent** **Row Pct** **Col Pct**	**Under 100 million**	**100+ million**	**Total**
< 155 million	7 5.5 29.17 58.33 63.64	5 6.5 20.83 41.67 38.46	12 50.00
155 million plus	4 5.5 16.67 33.33 36.36	8 6.5 33.33 66.67 61.54	12 50.00
Total	11 45.83	13 54.17	24 100.00

Statistic	**DF**	**Value**	**Prob**
Chi-Square	1	1.5105	0.2191

Explanation:

The p-value of 0.2191 is greater than the significance level of 0.05; therefore, the null hypothesis is accepted. This indicates that there is not a statistically significant association between estimated dollars spent through Medicaid allocated to off-label use and the settlement amount.

Hypothesis U:

As the estimated IMS dollars allocated to off-label use increases, the settlement amount increases.

Table of TotDolOff by AdjTotSettle			
TotDolOff	**AdjTotSettle**		
Frequency Expected Percent Row Pct Col Pct	**Under 100 million**	**100+ million**	**Total**
< 2 billion	7 5.2174 30.43 58.33 70.00	5 6.7826 21.74 41.67 38.46	12 52.17
2 billion+	3 4.7826 13.04 27.27 30.00	8 6.2174 34.78 72.73 61.54	11 47.83
Total	10 43.48	13 56.52	23 100.00

Statistic	DF	Value	Prob
Chi-Square	1	2.2531	0.1333

Fisher's Exact Test	
Cell (1,1) Frequency (F)	7
Left-sided Pr <= F	0.9740
Right-sided Pr >= F	0.1402
Table Probability (P)	0.1142
Two-sided Pr <= P	0.2138

Explanation:

The Chi-square p-value of 0.1333 and Fischer's Exact p-value of 0.1142 are greater than the significance level of 0.05; therefore, the null hypothesis is accepted. This indicates that there is not a statistically significant association between estimated IMS dollars allocated to off-label use and the settlement amount.

III. Mantel-Haenszel Chi-square tests

Based on results from the traditional Chi-square tests, I explored the significance of some of the findings using the Mantel-Haenszel test. If a variable was significant, an additional analysis utilizing Mantel-Haenszel Chi-square tests was conducted to determine if covariation between that factor, the independent variable "promotional dollars" and the dependent variable "adjusted total settlement amount" could be demonstrated. This will partition any significant Chi-square values into component values. Mantel-Haenzel tests were conducted for the significant results observed through the Chi-square tests: total estimated utilization (measured in IMS units) allocated to non-evidence base use; total estimated utilization (measured in IMS units) allocated to off-label use; total estimated Medicaid dollars allocated to non-evidence based use). A Mantel-Haenzel test was also used to test the association between the rate of off-label use and total settlement amount and the rate of non-evidence based use and total settlement amount. I hypothesized that the rates of off-label and non-evidence based use might show a statistically significant associations with settlement amount once promotion dollars are controlled.

Given that the settlements result from marketing schemes, I selected promotional dollars as the controlling variable. The Mantel-Haenszel controls for the independent

variable “promotional dollars” while examining the relationship between the significant variable and dependent variable “adjusted total settlement amount.”

H_w: As the rate of non-evidence based use increases, the adjusted settlement amount will increase when dollars spent on promotion are controlled.

Cochran-Mantel-Haenszel Statistics (Based on Table Scores)				
Statistic	**Alternative Hypothesis**	**DF**	**Value**	**Prob**
3	**General Association**	1	0.7035	0.4016

NdtiNonClinicalRate by AdjTotSettle			
Controlling for PromoDollars=Under 50 million			
NdtiNonClinicalRate	**AdjTotSettle**		
Frequency Expected Percent Row Pct Col Pct	**Under 100 million**	**100+ million**	**Total**
less than .39	4 3.7692 30.77 57.14 57.14	3 3.2308 23.08 42.86 50.00	7 53.85
.39 or greater	3 3.2308 23.08 50.00 42.86	3 2.7692 23.08 50.00 50.00	6 46.15
Total	7 53.85	6 46.15	13 100.00

Statistic	DF	Value	Prob
Chi-Square	1	0.0663	0.7968

Fisher's Exact Test	
Cell (1,1) Frequency (F)	4
Left-sided Pr <= F	0.7914
Right-sided Pr >= F	0.6166
Table Probability (P)	0.4079
Two-sided Pr <= P	1.0000

NdtiNonClinicalRate by AdjTotSettle			
Controlling for PromoDollars=50+ million			
NdtiNonClinicalRate	**AdjTotSettle**		
Frequency **Expected** **Percent** **Row Pct** **Col Pct**	**Under 100 million**	**100+ million**	**Total**
less than .39	3 2.1818 27.27 50.00 75.00	3 3.8182 27.27 50.00 42.86	6 54.55
.39 or greater	1 1.8182 9.09 20.00 25.00	4 3.1818 36.36 80.00 57.14	5 45.45
Total	4 36.36	7 63.64	11 100.00

Fisher's Exact Test	
Cell (1,1) Frequency (F)	3
Left-sided Pr <= F	0.9545
Right-sided Pr >= F	0.3485
Table Probability (P)	0.3030
Two-sided Pr <= P	0.5455

Statistic	DF	Value	Prob
Chi-Square	1	1.0607	0.3031

Explanation:

The M-H general association is not significant with a p=0.4061. The null hypothesis is accepted and the working hypothesis rejected. When promotional dollars are controlled, there is no association between the rate of non-evidence based use and adjusted settlement amount. For the group of drugs with promotional spending under 50 million dollars, the p=0.7968. For the group of drugs with promotional spending above 50 million, the p=0.3031.

H_w: As the rate of off-label use increases, the adjusted settlement amount will increase when dollars spent on promotion are controlled.

Cochran-Mantel-Haenszel Statistics (Based on Table Scores)				
Statistic	**Alternative Hypothesis**	**DF**	**Value**	**Prob**
	General Association	1	9.3730	0.0022

NdtiOffRegRate by AdjTotSettle			
Controlling for PromoDollars=Under 50 million			
NdtiOffRegRate	**AdjTotSettle**		
Frequency **Percent** **Row Pct** **Col Pct**	**Under 100 million**	**100+ million**	**Total**
less than .7	6 46.15 75.00 85.71	2 15.38 25.00 33.33	8 61.54
.7 or greater	1 7.69 20.00 14.29	4 30.77 80.00 66.67	5 38.46
Total	7 53.85	6 46.15	13 100.00

Statistic	DF	Value	Prob
Chi-Square	1	3.7452	0.0530

Fisher's Exact Test	
Cell (1,1) Frequency (F)	6
Left-sided Pr <= F	0.9953
Right-sided Pr >= F	0.0862
Table Probability (P)	0.0816
Two-sided Pr <= P	0.1026

NdtiOffRegRate by AdjTotSettle			
Controlling for PromoDollars=50+ million			
NdtiOffRegRate	AdjTotSettle		
Frequency Percent Row Pct Col Pct	Under 100 million	100+ million	Total
less than .7	3 27.27 100.00 75.00	0 0.00 0.00 0.00	3 27.27
.7 or greater	1 9.09 12.50 25.00	7 63.64 87.50 100.00	8 72.73
Total	4 36.36	7 63.64	11 100.00

Statistic	DF	Value	Prob
Chi-Square	1	7.2188	0.0072

Fisher's Exact Test	
Cell (1,1) Frequency (F)	3
Left-sided Pr <= F	1.0000
Right-sided Pr >= F	0.0242
Table Probability (P)	0.0242
Two-sided Pr <= P	0.0242

The M-H general association is significant with a p=0.0022. The null hypothesis is rejected and the working hypothesis accepted in the direction hypothesized. When promotional dollars are controlled, there is a significant association between the rate of off-label use and adjusted settlement amount. For the group of drugs with promotional spending under 50 million dollars, the adjusted settlement amount was greater for those drugs that had a rate of off-label use at or above 70%. The counterfactual was also true. This group produced a p=0.0530. An even stronger trend was observed for the group of drugs with promotional spending above 50 million dollars. The adjusted settlement amount was greater for those drugs that had a rate of off-label use at or above 70%. This group produced a p=0.0072.

H_w: As the estimated utilization (measured in IMS units) allocated to non-evidence based use increases, the adjusted settlement amount will increase when dollars spent on promotion are controlled.

Cochran-Mantel-Haenszel Statistics (Based on Table Scores)				
Statistic	**Alternative Hypothesis**	**DF**	**Value**	**Prob**
	General Association	1	5.9298	0.0149

AdjTotSettle by UnitClin			
Controlling for PromoDollars=Under 50 million			
AdjTotSettle	**UnitClin**		
Frequency Expected Percent Row Pct Col Pct	**< 200 million**	**200 million plus**	**Total**
Under 100 million	6 5 50.00 100.00 60.00	0 1 0.00 0.00 0.00	6 50.00
100+ million	4 5 33.33 66.67 40.00	2 1 16.67 33.33 100.00	6 50.00
Total	10 83.33	2 16.67	12 100.00

Statistic	DF	Value	Prob
Chi-Square	1	2.4000	0.1213

AdjTotSettle by UnitClin			
Controlling for PromoDollars=50+ million			
AdjTotSettle	UnitClin		
Frequency Expected Percent Row Pct Col Pct	< 200 million	200 million plus	Total
Under 100 million	2 0.7273 18.18 50.00 100.00	2 3.2727 18.18 50.00 22.22	4 36.36
100+ million	0 1.2727 0.00 0.00 0.00	7 5.7273 63.64 100.00 77.78	7 63.64
Total	2 18.18	9 81.82	11 100.00

Statistic	DF	Value	Prob
Chi-Square	1	4.2778	0.0386

The M-H general association is significant with a p=0.0149. The null hypothesis is rejected and the working hypothesis accepted in the direction hypothesized. When promotional dollars are controlled, there is a significant association between the estimated utilization (measured in IMS units) allocated to non-evidence based use and adjusted settlement amount. However, for the group of drugs with promotional spending under 50 million dollars, there was not a statistically significant association between adjusted settlement amount and estimated utilization (measured in IMS units) allocated to non-evidence based use. This group produced a p=0.1213. Conversely, the group of drugs where promotional spending was over 50 million dollars yielded a statistically

significant association. The group produced a p=0.0386 and the contingency table values were in the direction of the working hypothesis. The higher estimated units allocated to non-evidence based use the higher the adjusted settlement amount. The counterfactual was also true.

H_w: As the estimated utilization (measured in IMS units) allocated to off-label use increases, the adjusted settlement amount will increase when dollars spent on promotion are controlled.

Cochran-Mantel-Haenszel Statistics (Based on Table Scores)				
Statistic	Alternative Hypothesis	DF	Value	Prob
	General Association	1	4.7148	0.0299

AdjTotSettle by UnitOff			
Controlling for PromoDollars=Under 50 million			
AdjTotSettle	UnitOff		
Frequency Expected Percent Row Pct Col Pct	< 400 million	400 million plus	Total
Under 100 million	6 5.5 50.00 100.00 54.55	0 0.5 0.00 0.00 0.00	6 50.00
100+ million	5 5.5 41.67 83.33 45.45	1 0.5 8.33 16.67 100.00	6 50.00
Total	11 91.67	1 8.33	12 100.00

Statistic	DF	Value	Prob
Chi-Square	1	1.0909	0.2963

Fisher's Exact Test	
Cell (1,1) Frequency (F)	6
Left-sided Pr <= F	1.0000
Right-sided Pr >= F	0.5000
Table Probability (P)	0.5000
Two-sided Pr <= P	1.0000

AdjTotSettle by UnitOff			
Controlling for PromoDollars=50+ million			
AdjTotSettle	**UnitOff**		
Frequency Expected Percent Row Pct Col Pct	**< 400 million**	**400 million plus**	**Total**
Under 100 million	2 0.7273 18.18 50.00 100.00	2 3.2727 18.18 50.00 22.22	4 36.36
100+ million	0 1.2727 0.00 0.00 0.00	7 5.7273 63.64 100.00 77.78	7 63.64
Total	2 18.18	9 81.82	11 100.00

Statistic	DF	Value	Prob
Chi-Square	1	4.2778	0.0386

The M-H general association is significant with a p=0.0299. The null hypothesis is rejected and the working hypothesis accepted in the direction hypothesized. When promotional dollars are controlled, there is a significant association between the

estimated utilization (measured in IMS units) allocated to off-label use and adjusted settlement amount. However, similar to the results for estimated IMS units allocated to non-evidence based use for the group of drugs with promotional spending under 50 million dollars there was not a statistically significant association between adjusted settlement amount and estimated IMS units allocated to off-label use. This group produced a p=0.2963. For the group of drugs with promotional spending above 50 million dollars, there was a statistically significant association and in the direction of the working hypothesis. The group produced a p=0.0386.

H_w: As the estimated total Medicaid dollars allocated to non-evidence based use increases, the adjusted settlement amount will increase when dollars spent on promotion are controlled.

Cochran-Mantel-Haenszel Statistics (Based on Table Scores)				
Statistic	**Alternative Hypothesis**	**DF**	**Value**	**Prob**
	General Association	1	2.8415	0.0919

AdjTotSettle by MedDolCLin			
Controlling for PromoDollars=Under 50 million			
AdjTotSettle	**MedDolCLin**		
Frequency Expected Percent Row Pct Col Pct	**< 140 million**	**140 million+**	**Total**
Under 100 million	5 4 41.67 83.33 62.50	1 2 8.33 16.67 25.00	6 50.00
100+ million	3 4 25.00 50.00 37.50	3 2 25.00 50.00 75.00	6 50.00
Total	8 66.67	4 33.33	12 100.00

Statistic	DF	Value	Prob
Chi-Square	1	1.5000	0.2207

Fisher's Exact Test	
Cell (1,1) Frequency (F)	5
Left-sided Pr <= F	0.9697
Right-sided Pr >= F	0.2727
Table Probability (P)	0.2424
Two-sided Pr <= P	0.5455

AdjTotSettle by MedDolCLin			
Controlling for PromoDollars=50+ million			
AdjTotSettle	**MedDolCLin**		
Frequency Expected Percent Row Pct Col Pct	**< 140 million**	**140 million+**	**Total**
Under 100 million	2 1.0909 18.18 50.00 66.67	2 2.9091 18.18 50.00 25.00	4 36.36
100+ million	1 1.9091 9.09 14.29 33.33	6 5.0909 54.55 85.71 75.00	7 63.64
Total	3 27.27	8 72.73	11 100.00

Statistic	DF	Value	Prob
Chi-Square	1	1.6369	0.2008

Fisher's Exact Test	
Cell (1,1) Frequency (F)	2
Left-sided Pr <= F	0.9758
Right-sided Pr >= F	0.2788
Table Probability (P)	0.2545
Two-sided Pr <= P	0.4909

The M-H general association was not significant with a p=0.0919. The null hypothesis is accepted and the working hypothesis rejected. Although there was a significant association between estimated total Medicaid dollars allocated to non-evidence based use and adjusted settlement amount with the traditional Chi-square tests, it appears controlling for promotional dollars eliminates this association.

For the group with promotional dollars spent under 50 million dollars, the p=0.2207. For the group with promotional dollars spent above 50 million dollars, the p=0.2008. The contingency tables for both groups revealed trends moving in the direction of the working hypothesis (the larger the estimated Medicaid dollars allocated to non-evidence based use, the larger the settlement amount), but not to a significant degree.

Other:

Other M-H tests using these variables revealed insignificant results. There was no association between adjusted settlement amount and promotional dollars controlling for the following: ratio of non-evidence based use relative to all uses (p-value=0.4016); (total estimated Medicaid dollars allocated to off-label use (p-value= 0.4465); estimated

Medicaid units allocated to non-evidence based use (p=0.1727); estimated Medicaid units allocated to off-label use (p=0.1727). **Table L** shows the categorization of each variable used for the Mantel-Haenszel tests and resulting p-values.

CHAPTER 5

DISCUSSION

The preceding chapter presents the results of statistical analysis using data collected from a variety of sources. The independent variables were identified through a qualitative analysis of each lawsuit and drug involved. The dependent variable was total settlement amount. This chapter presents a discussion of the results and the conclusions to be made from them as they related to the primary variable of interest to this study, drugs involved in settlements related to marketing schemes such as off-label promotion and/or kickbacks orchestrated by pharmaceutical companies. This is followed by recommendations for future research on this topic.

The primary premise of this research was that the total settlement amounts do not deter a given pharmaceutical company from implementing future marketing schemes such as off-label promotion because the companies still make more money from promoting the products off-label compared to if the company did not promote off-label. The sample size was too small to make any concrete conclusions concerning the stated premise, but the trends and associations observed suggest that there is no association between settlement amounts and dollars. Furthermore, the qualitative findings show settlements involving off-label promotion are increasing in number. The increase in settlements suggests companies are continuing to engage in off-label promotion of their products.

Results of the univariate descriptive statistics for each continuous independent variable and the settlement amounts demonstrated considerable variance and range.

These results support the use of nonparametric statistical analysis. In terms of the dependent variable "total settlement amount" both the highest and lowest settlement amounts were for the only two drugs withdrawn from the market due to safety reasons. This suggests that market withdrawal may not have any bearing on settlement amounts. A sample size of two certainly does not merit drawing conclusions on cause and effect, but it is interesting that the available press releases and Complaint relating to each settlement emphasized the withdrawal of both drugs in part based on the use of each drug for non-evidence based use. Assuming some of this use could have been avoided had the drug not been promoted using allegedly illegal marketing schemes and that settlement amounts are influenced by the potential harm associated with illegal marketing schemes, then one might expect both cases to be closer to the higher end of settlement amounts.

Baycol generated the lowest settlement amount but also had one of the lower totals for Medicaid dollars (21st out of 23 drugs) and total IMS dollars (18th out of 24 drugs). Baycol also had the lowest rate of off-label and non-evidence based use relative to all uses, which may have contributed to the low settlement amount. Bextra generated the highest settlement amount but was in the middle in terms of total Medicaid sales (11th out of 23 drugs) and total IMS dollar sales (11th out of 24 drugs). The results of these two examples are not surprising considering the Chi-square tests showed lack of a statistically significant association between any standalone variable (where two data sources are not used as one variable) and total settlement amount.

Interestingly, the average total settlement amount across all drugs was about 12.6% of the total IMS dollars sold in the pre-settlement timeframe and 166% of the total

Medicaid dollars sold in the pre-settlement timeframe. One would expect that the settlement amount would be more related to Medicaid dollars than non-Medicaid given the fact that these lawsuits are intended to recover money spent by the government (i.e., Medicaid and Medicare) for prescription drugs due to off-label promotion. However, within the sample of drugs involving settlements related to marketing schemes such as off-label promotion and/or kickbacks, no statistically significant association existed between total settlement amount and total IMS/Medicaid dollars or units pre-settlement.

Figure IIa shows the ratio of settlement amount relative to total IMS dollars and Medicaid dollars for each drug. Figure IIb shows the results without Bextra, Intron A, Trisenox, and Xyrem. Figure IIa shows that the ratio of settlement amount per Medicaid dollars for Bextra, Intron A, Trisenox, and Xyrem is extremely high in relation to the other drugs. Besides these four drugs and Serostim, every other ratio is below one as shown in Figure IIb. Thus, the Figure shows that the majority of settlements are much lower than the amount spent for the drug through Medicaid. The high ratio of settlement per Medicaid dollars for Bextra, Xyrem, Trisenox, Intron A and Serostim is likely to be attributable to other factors rather than suggesting a trend towards greater settlement amounts relative to Medicaid dollars.[586]

The Bextra settlement involved multiple drugs. As part of the settlement, Pfizer agreed to pay a criminal penalty of 1.3 billion dollars for off-label promotion involving Bextra. The civil portion of the settlement involved several other Pfizer drugs, but Bextra was the only one that had been withdrawn from the market. It is likely that the

[586] For example, Medicare Part A, B and D data was not available. Medicare Part A and B would reflect a larger percentage of injectables because they are often administered in the hospital or clinic setting.

pharmaceutical company would rather allocate a larger proportion of the settlement amount to a drug that is no longer on the market than to those still commercially available.

Xyrem is also a unique situation in that it has a very limited distribution chain where only certain specialty pharmacies may dispense it. For this reason, it is plausible that Xyrem was reimbursed through channels of distribution that were not reflected in the outpatient Medicaid dollars represented by CMS, and thus, may be underinflated leading to a higher ratio.

The other drugs with higher ratios of settlement amount to Medicaid dollars are injectables. Injectables are often times administered in a clinic or hospital setting and thus paid for through the patient's medical benefits, Medicare Part A or Part B. This study did not include reimbursement through medical benefits, Medicare Part A or Part B. The following sampled drugs are injectables: Intron A, Genotropin, Actimmune, Trisenox and Serostim. Of these injectables, Intron A, Trisenox and Serostim had ratios above one. Thus, the ratios of settlement amount relative to Medicaid dollars higher than one are highly likely to be due to other factors such as channel of distribution and site of use rather than a showing that the government is recovering more than what it spent on any given drug through settlement.

The ratios of settlement amount relative to IMS total dollars were all less than one indicating that the total dollars reimbursed for the drugs far outweighed the settlement amount as shown in Figures IIa, IIb and IIc. The IMS database used represented

additional channels of distribution that was likely to include some sales not represented with the Medicaid data.

It is certainly important to note that these dollar amounts do not take into account rebates or chargebacks so the sales dollars from both IMS and Medicaid are inflated. Since no rebates were taken out and there is nothing to suggest rebate amounts would be disproportionately allocated between drugs, trends and testing associations between these variables would likely exist similarly had net rather than gross sales been utilized. It is also important to note that not all Medicaid sales are due to the allegedly illegal marketing schemes. Nevertheless, without the five drugs with unique situations, the settlement amounts are much less than the amount the government spent on the drug during the pre-settlement timeframe.

In terms of statistical tests of association between dollars and units and the settlement amounts, the Chi-square results showed few significant associations. There was no statistically significant association between adjusted settlement amount and the following continuous variables: total IMS dollars, total IMS units, total Medicaid dollars, total Medicaid units, dollars spend on promotion, the rate of off-label use relative to total uses, and the rate of non-evidence based use relative to total uses.

Since the government is only recovering for government dollars and units that resulted from off-label promotion, perhaps it is not surprising that no association existed between total IMS dollars and units since this includes all sales rather than just sales paid for by the government. On the other hand, if the goal is to deter and punish a company for off-label promotion or other illegal marketing schemes such as kickbacks to

physicians, it could be argued that the settlement amounts should be directly related to overall total sales of the drug.

Total Medicaid dollars and utilization (measured in Medicaid units) also showed no significant association with total settlement amount. Although all sales or units are not attributable to questionable marketing schemes, these results do suggest that overall Medicaid sales and units do not necessarily influence the size of the settlement amount. That is, drugs representing a large amount of Medicaid dollars or units compared to a drug representing a smaller amount will not necessarily result in a larger settlement amount. This suggests other factors besides Medicaid dollars or utilization contribute to settlement amount. Additionally, it supports the primary premise of this study that settlement amounts are not an effective deterrent.

Considering the sample is settlement amounts involving allegedly illegal marketing and promotional schemes, one would expect companies who spent the most money on promotion of their drug to also have larger settlement amounts by virtue of the fact that the settlements involved off-label *promotion* of the drug or kickbacks encouraging use of the drug. Presumably, the more money spent on promoting the product, the more spent on promoting off-label uses or providing kickbacks, and therefore, the more likely the government collects a larger settlement due to increased sales resulting from the marketing scheme. However, no association existed between total promotion and total settlement amount.

Lastly, considering the selected sample, one might expect that the settlement amounts would be related to the rate of off-label use relative to total uses and/or the rate

of non-evidence based use to total uses. On the other hand, just because a drug is used off-label does not necessarily mean the company selling it promoted the drug for that off-label use. As discussed above in the literature review, off-label prescribing is not necessarily illegal, and it is a common practice utilized by most prescribers. A statistically significant association did not exist between settlement amount and the rate of off-label use or non-evidence based use. This result suggests that drugs used more frequently for off-label uses are not significantly associated with a higher settlement amount. For instance, the drugs with the highest percentage of off-label use, Neurontin and Gabitril garnered settlement amounts that were 6 out of 24 and 12 out of 24, respectively.

No statistically significant associations existed between the total settlement amount and any of the nominal variables. Results of the Chi-square tests showed no association between adjusted settlement amount and the following nominal variables: FDA warning letters, black box warnings, black box warnings that related to one of the alleged off-label uses, or the number of indications. Although there was some indication from the case studies and literature surrounding each lawsuit that the number of FDA warning letters relating to a given drug or a black box warning related to the alleged off-label use may have influenced the amount recovered, the results suggest that this information did not impact settlement amounts. At least in the sample tested, these variables had no association with the total settlement amount.

Given the fact that the sample was settlements involving off-label promotion, further analysis of the continuous variables as a percent of off-label use and non-evidence

based use was conducted. First with traditional Chi-square tests and then for the statistically significant associations, with Mantel-Haenszel Chi-square tests. Here, statistically significant associations resulted from testing whether an association exists between the settlement amount and the following: estimated dollars spent through Medicaid allocated to non-evidence based use, total estimated utilization (measured in units through IMS) allocated to non-evidence based use, and total estimated utilization (measured in units through IMS) allocated to off-label use. **Table F** shows the p-values for each variable.

In terms of Medicaid dollar sales and units sold as a proportion of off-label and non-evidence based use, the Chi-square tests suggested that there is an association between settlement amounts and dollars through Medicaid, but only for estimated dollars allocated to non-evidence based use. The p-value was 0.0405. The trends observed from the contingency tables demonstrate that as the group of drugs with a high rate of sales dollars through Medicaid attributable to non-evidence based use increased, the total settlement amounts also increased. This result suggests that drugs were more likely to result in a higher total settlement if prescribed for uses where evidence of efficacy and/or safety is lacking.

Interestingly, a similar trend was not present with total estimated Medicaid dollars allocated to off-label uses. In terms of Medicaid, the tests suggest that non-evidence based use is a more predominant factor in settlement amounts than off-label use. On the other hand, the tests of estimated utilization (measured in Medicaid units) allocated to non-evidence based use and off-label use yielded insignificant results.

Compared to Medicaid dollars and units, the IMS dollar and utilization allocated to off-label use and non-evidence based use yielded nearly completely opposite results. Here, the tests of association between total settlement amount and total estimated IMS dollars allocated to off-label use and to non-evidence based use yielded insignificant associations. Whereas the tests of association between total settlement amount and total estimated utilization (measured in IMS units) allocated to off-label use and non-evidence based use yielded p-values of 0.0464 and 0.0191, respectively. These results suggest that units are a more reliable predictor of total settlement amount than total dollars except that the Medicaid test results for utilization (measured as units) were not significant. It is not clear why IMS utilization (measured as units) allocated to off-label use and non-evidence based use would result in a significant association with settlement amounts, but Medicaid utilization allocated to off-label use and non-evidence based use would not.

To evaluate the significant findings further, I used the Mantel-Haenszel test. Considering all drugs sampled related to a marketing scheme (i.e., off label promotion or kickbacks), I used promotional dollars as the controlling independent variable. One might expect that concentrating the sample into the group of drugs where the pharmaceutical company spent a large amount on promotion and the group of drugs where the pharmaceutical company spent a smaller amount on promotion would allow for further analysis of the traditional Chi-square test results.

Controlling for promotional dollars spent revealed a significant general association between settlement amount and utilization (measured as IMS units) allocated to off-label ($p=0.0022$) and to non-evidence based use ($p=0.0149$), but no association

existed with Medicaid dollars allocated to non-evidence based use. There is a significant relationship between total settlement amount relative to IMS units allocated to off-label and non-evidence based uses when dollars spent on promotion is greater than 50 million. In the group where dollars spent on promotion is less than 50 million, a significant association between settlement amount and off-label and non-evidence based use did not exist. Thus, the significant general association findings resulted from a strong association seen in the groups with more money spent on promotion.

These results along with the qualitative findings demonstrate trends consistent with the primary premise of this study: settlement amounts do not appear to have a deterrent effect based on the assumption that companies likely make more using marketing schemes that the government alleges are illegal. Based on the nonparametric tests utilized, the only consistent associations involved settlement amounts and units (IMS) allocated to off-label use and non-evidence based use, rather than total dollars or total units. Further, no statistically significant results existed for Medicaid dollars and units. At the same time, taking into account the amount of off-label use and/or non-evidence based use, the total IMS utilization (measured in units) is associated with settlement amount and in a positive direction. The results suggest that overall utilization (measured in units) may impact settlement amounts when estimates on the amount of off-label or non-evidence based use is taken into account. Additionally, there are an increasing number of settlements based on the qualitative findings of this study, which suggests settlement amounts are not preventing companies from engaging in questionable marketing schemes.

IMS units were much more representative of overall units sold in the U.S., which may explain the significant associations with settlement amount when the units were allocated to off-label and evidence-based use than Medicaid units. The results suggest the need for replicating the analysis with a larger sample size where researchers could utilize parametric statistics such as MLR to analyze the relevance of multiple potential variables in determining settlement amount. While the results of this study suggest that settlement amounts are not associated with total dollars (IMS and Medicaid) collected by the pharmaceutical company for its drug, the contingency tables did show movement in the direction of a possible association had a larger sample size been available.

Recommendations for future research

The findings of this study suggest exploration of several research topics and are offered here in the hopes of furthering research in this area:

1) The overall trends of estimated Medicaid dollars and utilization (measured in units) allocated to off-label use and non-evidence based use compared to settlement amounts warrants further study. The fact that significant results occurred in traditional Chi-square tests but were not present with the Mantel-Haenszel test suggest that a larger sample size may yield differing results.

2) This research focused on total dollars and units measured from two data sources where actual net sales were not available. Conducting an analysis with actual net sales is ideal, albeit likely to be impossible given the proprietary nature of such data.

Nevertheless, a study using actual net sales compared to settlement amounts would provide more accurate results.

3) This research focused on settlements involving marketing schemes. There is a need, however, to examine all health care fraud settlements involving pharmaceutical companies.

4) This research focused on settlements through mid-2010, but several settlements have occurred since this time. This alone would increase the sample size and possibly create enough sampling power to perform parametric analysis using multi-linear regression.

5) This research used the AHFS DI® for information on non-evidence based uses for each drug. Replicating the study using another data source such as Thomson Reuter's Micromedix strength of evidence categories for non-evidence based use may yield different results.

Limitations of the Study

This study has several substantial limitations, and therefore, although the results provide some support for the primary premise, a larger sample size and actual net sales or a means of accurately estimating the prescriptions attributable to marketing schemes could yield vastly different results.

By selecting health care fraud lawsuits ending in settlement that involve marketing schemes conducted by pharmaceutical companies between 1990 and mid-2010, selection bias is partially controlled. However, unintentional selection bias is possible because the study includes only cases that lead to settlement or verdict.

Research bias also exists in assigning uses as "non-evidence based." Depending on the cut-off for evaluating efficacy and safety evidence and the source used, assignment may vary. In an attempt to control for bias related to assigning "non-evidence based", the same source was utilized and AHFS did not change its criteria for evaluating clinical study results. AHFS is one of the few compendia relied on by government payors for information on off-label uses.

Using content analysis techniques to find other variables may raise questions about bias. The content analysis techniques rely upon the researcher's interpretation of the information, and while there are stopgap measures to reduce bias, the potential for interpretation related bias still exists. In an attempt to eliminate the potential for bias, the same information was collected for all drugs and from the same sources.

This study describes patterns, trends, and association but the occurrence of chance is still possible. There is also the possibility that spuriousness exists if the variables are more dependent upon or influenced by an untested variable. For instance, the research focused on publically available information and non-public information was not used, but could influence settlement amounts.

It is possible that bivariate associations may or may not be significant but when included in a more comprehensive analysis with a greater sample size of multiple variables, associations that were significant may turn out not to be significant and associations that were not significant will become significant.

By using multi-variate analyses, the variables will "compete" with one another among many variables. The Mantel-Haenszel tests attempted to ascertain the important

variables from non-important variables, but multiple test error may exist and is not completely avoidable. In a series of bivariate comparisons, there will always be significant associations that are spurious. It is possible that through multiple tests with differing variables, associations that turned out to be significant were merely by chance. Only select variables were tested further with the Mantel-Haenszel test to eliminate some of the spuriousness that could result.

This research also has data source limitations. First, there is no way to ensure the accuracy of the data obtained from outside sources, but the sources used are well-known and used within the pharmaceutical industry. IMS Health data sources are widely relied upon within the pharmaceutical industry for estimating drug sales and utilization. CMS is the only data source publicly available that collects dollars and units paid through the Medicaid program.

Second, there are limitations with the availability of data. The promotional dollars were only obtained for the timeframe of January 2003 through December 2009. Furthermore, there may be promotional dollars spent that the companies do not report to IMS. In both cases, the promotional dollars spent per drug is likely underestimated. However, the vast majority of allegations of off-label promotion occurred after 2002 so in terms of timeframes, the study included most of the promotional dollars that had the potential to be related to off-label promotion.

The Medicaid data source only included data through the second quarter of 2009. The last available quarter was then used as the data values for subsequent quarters, which could lead to over or underestimations of the actual total dollars and units from

subsequent quarters. However, given the timeframes were over multiple years, it is unlikely that the difference between actual and estimated data for one to four quarters would cause a material change in any of the results.

The pre-settlement period included all sales from when the drug entered the market to one-month prior to settlement. In the vast majority of cases, the actual timeframe where allegations of off-label promotion or kickbacks occurred was much smaller.

This research did not account for potential bias related to the legal proceeding itself. For instance, the sample did not test potential factors that influence settlements such as the filing district, the law firms involved, the factors involved with the investigation conducted by the government, and the government's involvement.

Unfortunately, using total dollar sales per pharmaceutical product fails to take into consideration the other litigation expenses besides the actual case settlement amount. Some of the costs a drug company may incur include: the cost to settle the case (or the cost of the jury verdict), attorney's fees and other fees, and the impact of the company's overall market value if investors grow skeptical of the company's ability to cover their losses or expenses related to litigation. There are also costs incurred for on-going research and development, marketing and promotional costs, and the initial cost of bringing the drug to market. Legal expenses and insurance payouts affect decisions about settlement amounts, but this information was not included in the study. On the other hand, these costs do not change total dollar sales.

Table A: Nominal Variables[587]

DrugName	BBstatus	BBpromo	Warning	Indications
Abilify	1	1	0	2
Actimmune	0	0	0	2
Actiq	1	1	1	1
Baycol	2	2	1	1
Bextra	0	0	1	3
Cardizem LA	0	0	0	2
Celexa	1	1	1	1
Evista	0	0	5	4
Gabitril	0	0	0	1
Genotropin	0	0	1	4
Intron A	1	0	0	6
Lexapro	1	1	0	2
Loprox	0	0	2	6
Neurontin	0	0	2	2
Oxycontin	1	1	2	1
Provigil	0	0	1	3
Seroquel	1	1	3	3
Serostim	0	0	0	1
TOBI	0	0	0	1
Temodar	0	0	1	3
Topamax	0	0	1	5
Trisenox	1	0	0	2
Xyrem	1	0	0	1
Zyprexa	1	1	0	7

[587] The statistical analysis did not include Protropin because there was insufficient information available for Protropin.

Table B-1: Miscellaneous Information from Case Studies

Genentech	Protropin		50,000,000		ND Cali
Pfizer Pharms	Neurontin	5/13/2004	430,000,000	8/13/1996	D Mass
Lilly	Evista	12/21/2005	36,000,000	12/21/2005	SD Indiana
EMD Serono	Serostim	10/17/2005	704,000,000	6/26/2002	D Mass
Schering	Temodar and Intron A	8/26/2006	435,000,000	7/12/2004	ED Pa
Intermune Pharms	Actimmune	10/26/2006	36,900,000	10/24/2004	ND Cali
Pharmacia and Upjohn [Pfizer]	Genotropin	4/13/2007	34,680,000	6/5/2003	D Mass
Purdue Pharma LP	Oxycontin	5/10/2007	634,515,475	09/27/2005	WD Virginia
Medicis	Loprox	5/8/2007	9,800,000	8/20/2004	Kansas
Cell Therapeutics [Cephalon]	Trisenox	4/17/2007	10,500,000	2/1/2006	WD WA
Jazz	Xyrem	7/13/2007	20,000,000	1/24/2005	ED NY
Biovail Labs Intl	Cardizem LA	10/1/2009	24,600,000	5/19/2008	D Mass
Bayer Pharms	Baycol	1/23/2007	8,000,000	10/05/2006	D NJ

Cephalon	Actiq and Gabitril and Provigil	11/14/2007	425,000,000	11/14/2003	ED Pa
Otsuka [Bristol-Myers Squibb]	Abilify (other drugs included in settlement)	9/28/2007	4,000,000 and 515,000,000	10/10/2006	D Mass
Lilly	Zyprexa	1/15/2009	1,415,000,000	02/19/2003	ED Pa
GD SEARLE [Pfizer]	Bextra (other drugs included in settlement)	9/2/2009	2,300,000,000	10/24/2005	D Mass
Forest Labs	Celexa and Lexapro (other drugs included in settlement)	9/15/2010	313,000,000	1/28/2005	D Mass
AstraZeneca	Seroquel	4/27/2010	520,000,000	7/22/2004	ED Pa
Ortho McNeil [Janssen]	Topamax	4/29/2010	81,000,000	8/5/2003	D Mass
Novartis Pharms	TOBI	5/4/2010	72,500,000	10/6/2006	ND Cali

Table B-2: Therapeutic Class for Each Drug

TOBI	Aminoglycosides
Provigil	Analeptics
Bextra	Antiarthritis / COX-2 Inhibitor
Loprox	Antifungal Misc
Temodar	Antineoplastic
Trisenox	Antineoplastic
Abilify	Antipsychotics
Zyprexa	Antipsychotics
Seroquel	Antipsychotics
Evista	Bone Density Regulator
Cardizem LA	Calcium Channel Blocker
Oxycontin	Codeine and Combination
Protropin	Growth Hormone/ Anabolic Hormone
Serostim	Growth Hormone/ Anabolic Hormone
Genotropin	Growth Hormone/ Anabolic Hormone
Baycol	HMG-CoA reductase inhibitor
Intron A	Immunologic
Actimmune	Immunologic
Actiq	Morphine / Opium derivative
Xyrem	Non-barbituate
Neurontin	Seizure Disorder
Gabitril	Seizure Disorder
Topamax	Seizure Disorder
Celexa	Selective Serotonin Reuptake Inhibitor
Lexapro	Selective Serotonin Reuptake Inhibitor

Table C: Off-Label Categorization and Rate[588]

DrugName	Reg0	Reg1	Reg6	Off-label use rate
Abilify	6,459,467	3,894,389	18,880	0.6239
Actimmune	18,426	0	0	1.0000
Actiq	193,967	50,515	0	0.7934
Baycol	250,952	4,625,818	19,241	0.0515
Bextra	19,366,352	4,133,639	101,549	0.8241
Cardizem LA	1,525,985	3,870,765	18,343	0.2828
Celexa	37,782,485	8,709,378	315,946	0.8127
Evista	6,598,924	5,094,772	148,621	0.5643
Gabitril	1,687,190	52,945	5,362	0.9696
Genotropin	91,494	358,633	0	0.2033
Intron A	240,373	457,529	0	0.3444
Lexapro	63,856,282	18,535,905	432,225	0.7750
Loprox	1,983,435	3,036,144	4,525	0.3951
Neurontin	23,247,628	290,783	130,980	0.9876
Oxycontin	72,779,220	15,924,814	413,164	0.8205
Provigil	3,698,935	833,708	46,417	0.8161
Seroquel	29,409,066	6,425,946	75,276	0.8207
Serostim	2,047	6,236	0	0.2471
Temodar	445,020	77,752	0	0.8513
TOBI	177,776	168,673	0	0.5131
Topamax	20,324,613	8,048,064	88,601	0.7163
Trisenox	9,804	10,165	0	0.4910
Xyrem	29,195	21,380	0	0.5773
Zyprexa	25,482,395	7,370,778	87,562	0.7756

[588] **Datasources: National Disease and Therapeutic Index ™**. The statements, findings, conclusions, views, and opinions contained and expressed in this dissertation are based in part on data obtained under license from the following IMS Health Incorporated information service(s): National Disease and Therapeutic Index™ (January 1998 through December 2009), Integrated Promotional Services ™ (January 2003 through December 2009), National Sales Perspectives ™ (January 1998 through December 2009). All Rights Reserved. The statements, findings, conclusions, views, and opinions contained and expressed herein are not necessarily those of IMS Health Incorporated or any of its affiliated or subsidiary entities.The categories are based on the indications as listed in the AHFS DI®.

Table D: Non-Evidence Based Categorization and Rate[589]

DrugName	NoEvid1	NoEvid3	NoEvid4	6	Non-evidence based use rate
Abilify	3,894,389	3,797,148	2,662,320	18,880	0.2571
Actimmune	0	0	18,426	0	1.0000
Actiq	50,515	0	193,967	0	0.7934
Baycol	4,625,818	52,188	198,764	19,241	0.0408
Bextra	4,133,639	2,741,833	16,624,519	101,549	0.7074
Cardizem LA	3,870,765	555,722	970,263	18,343	0.1798
Celexa	8,709,378	21,838,450	15,944,035	315,946	0.3429
Evista	5,094,772	1,475,320	5,123,604	148,621	0.4382
Gabitril	52,945	36,860	1,650,330	5,362	0.9484
Genotropin	358,633	5,166	86,328	0	0.1918
Intron A	457,529	17,888	222,485	0	0.3188
Lexapro	18,535,905	38,214,427	25,641,855	432,225	0.3112
Loprox	3,036,144	892,995	1,090,440	4,525	0.2172
Neurontin	290,783	1,429,489	21,818,139	130,980	0.9269
Oxycontin	15,924,814	5,758,784	67,020,436	413,164	0.7556
Provigil	833,708	323,884	3,375,051	46,417	0.7446
Seroquel	6,425,946	12,534,550	16,874,516	75,276	0.4709
Serostim	6,236	0	2,047	0	0.2471
Temodar	77,752	362,122	82,898	0	0.1586
TOBI	168,673	0	177,776	0	0.5131
Topamax	8,048,064	10,060,125	10,264,488	88,601	0.3618
Trisenox	10,165	8,412	1,392	0	0.0697
Xyrem	21,380	0	29,195	0	0.5773
Zyprexa	7,370,778	14,880,135	10,602,260	87,562	0.3227

[589] **Datasources: National Disease and Therapeutic Index ™**. The statements, findings, conclusions, views, and opinions contained and expressed in this dissertation are based in part on data obtained under license from the following IMS Health Incorporated information service(s): National Disease and Therapeutic Index™ (January 1998 through December 2009), Integrated Promotional Services ™ (January 2003 through December 2009), National Sales Perspectives ™ (January 1998 through December 2009). All Rights Reserved. The statements, findings, conclusions, views, and opinions contained and expressed herein are not necessarily those of IMS Health Incorporated or any of its affiliated or subsidiary entities.The categories are based on off-label information from AHFS DI®.

Table E: Study Variables

Variable Name	Measure	Operation
Dependent Variable		
Settlement amount	Source: settlement amount from Department of Justice Press Releases	Continuous variable with a value between 0 and infinity
Independent Variables		
Total IMS units	Source: IMS NSP Start with the month where Medicaid total units and NSP IMS total units exist and end at the month before settlement	Continuous variable with a value between 0 and infinity
Total IMS dollars	Source: IMS NSP Start with the month where Medicaid total dollars and NSP IMS total units exist and end at the month before settlement	Continuous variable with a value between 0 and infinity
Total Medicaid units	Source: CMS Start with the month where Medicaid total units and dollars exist and end at the month before settlement	Continuous variable with a value between 0 and infinity
Total Medicaid dollars	Source: IMS NSP Start with the month where Medicaid total units and total dollars exist and end at the month before settlement	Continuous variable with a value between 0 and infinity
Estimated Medicaid units allocated to off-label use	Source: CMS and NDTI Start with the month where Medicaid total units and total dollars exist and end at the month before settlement	Continuous variable with a value between 0 and infinity
Estimated Medicaid dollars allocated to off-label use	Source: CMS and NDTI Start with the month where Medicaid total units and total dollars exist and end at the month before settlement	Continuous variable with a value between 0 and infinity
Estimated Medicaid units allocated to non-evidence based use	Source: CMS and NDTI Start with the month where Medicaid total units and total dollars exist and end at the month before settlement	Continuous variable with a value between 0 and infinity

Estimated Medicaid dollars allocated to non-evidence based use	Source: CMS and NDTI Start with the month where Medicaid total units and total dollars exist and end at the month before settlement	Continuous variable with a value between 0 and infinity
Estimated IMS units allocated to off-label use	Source: IMS NSP and NDTI Start with the month where Medicaid total units and NSP IMS total dollars exist and end at the month before settlement	Continuous variable with a value between 0 and infinity
Estimated IMS dollars allocated to off-label use	Source: IMS NSP and NDTI Start with the month where Medicaid total units and NSP IMS total dollars exist and end at the month before settlement	Continuous variable with a value between 0 and infinity
Estimated IMS dollars allocated to non-evidence based use	Source: IMS NSP and NDTI Start with the month where NSP IMS total units and NSP IMS total dollars exist and end at the month before settlement	Continuous variable with a value between 0 and infinity
Estimated IMS units allocated to non-evidence based use	Source: IMS NSP and NDTI Start with the month where Medicaid total units and NSP IMS total dollars exist and end at the month before settlement	Continuous variable with a value between 0 and infinity
Total promotional spend	Source: IMS IPS Start in 2003 and end at the month before settlement	Continuous variable with a value between 0 and infinity
Estimated promotion allocated to off-label use	Source: IMS IPS and NDTI Start in 2003 and end at the month before settlement	Continuous variable with a value between 0 and infinity
Estimated promotion allocated to non-evidence based use	Source: IMS IPS and NDTI Start in 2003 and end at the month before settlement	Continuous variable with a value between 0 and infinity
Off-label use relative to total uses	Source: IMS NDTI Total number of uses reported for off-label use relative to total number of uses	Continuous variable with a value between 0 and 1

Non-evidence based use relative to total uses	Source: IMS NDTI Total number of scripts for non-evidence based use (no evidence or the evidence has not been established (4) and/or harmful (2)) relative to all uses	Continuous variable with a value between 0 and 1

Table E-2: Schematic of Study Variables

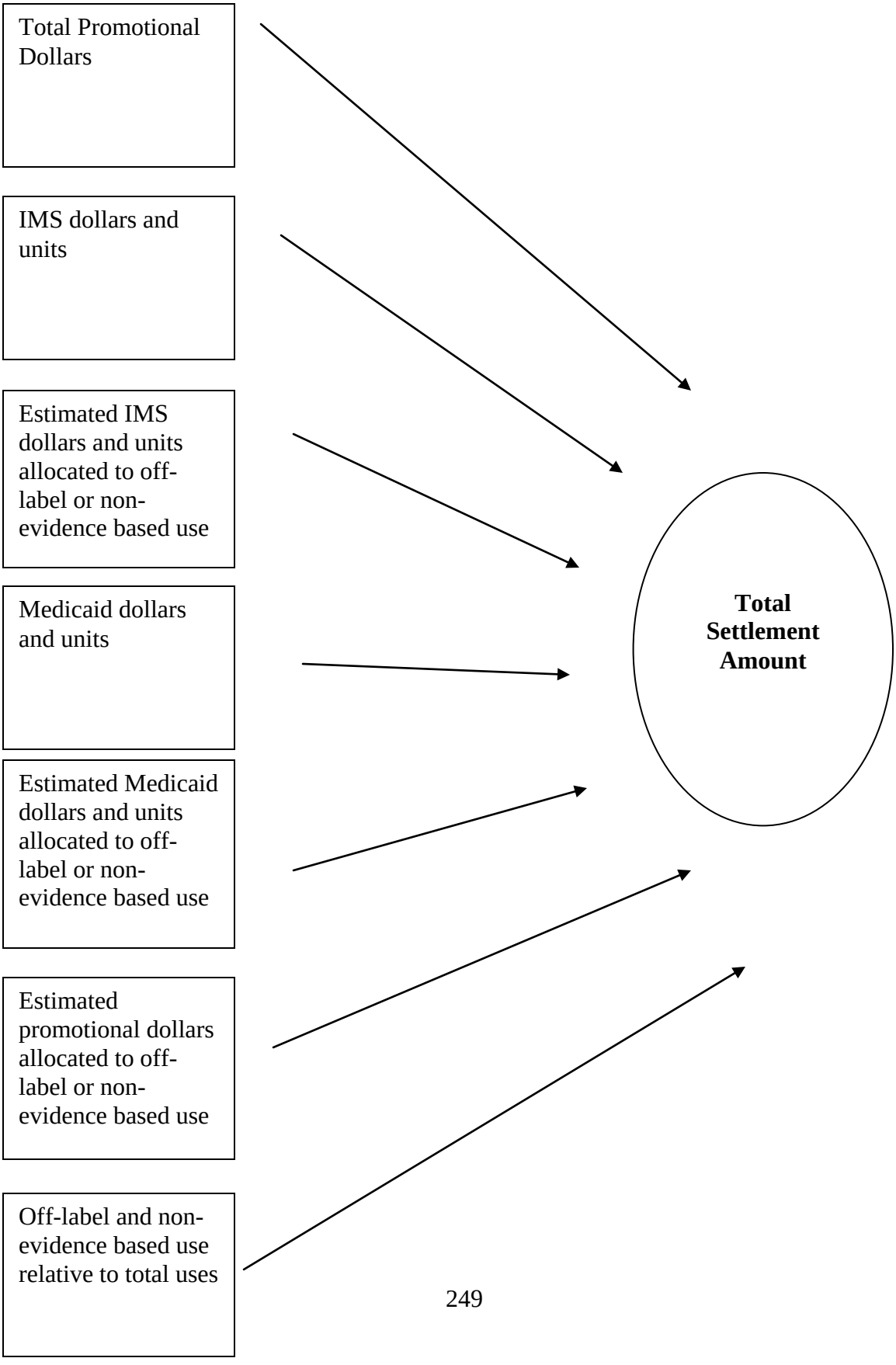


Table F: Univariate Statistics with p-values[590,591]

Variable	Mean	Std Dev	Range Spread	N	Chi-Square p-value
AdjTotSettle	329,308,301	538,668,509	2,292,000,000	23	na
Units	1,974,437,051	2,767,029,442	9,728,021,560	23	0.5800
TotalDollars	5,735,672,165	7,332,739,145	25,773,700,000	23	0.1610
TotalDollarsOFF	4,386,585,808	5,949,170,868	20,056,600,000	23	0.1333
UnitOFF	1,583,503,612	2,473,697,280	9,608,520,125	23	0.0464
TotalDollarsNoEvid	2,640,816,205	3,339,248,801	10,803,400,000	23	0.0619
UnitNoEvid	1,054,261,089	1,979,336,038	9,018,341,139	23	0.0191
AdjTotSettle	316,420,455	530,598,025	2,292,000,000	24	na
MedDollars	1,455,428,857	2,886,408,989	12,533,400,000	24	0.1883
MedUnit	372,553,445	623,964,072	2,097,361,405	24	0.1883
PromoDollars	406,193,389	731,634,233	3,171,773,141	24	0.3917
Off-label Rate	0.63569	0.26734	0.94854	24	0.2668
NoEvidenceRate	0.45397	0.28774	0.95924	24	0.3917
MedDollarsOFF	1,117,391,746	2,283,929,680	9,721,684,847	24	0.2191
MedDollarsNoEvid	624,984,417	1,110,482,285	4,044,922,416	24	0.0405
MedUnitOFF	304,292,693	542,655,665	1,878,277,763	24	0.0932
MedUnitNoEvid	197,685,016	405,119,489	1,762,795,818	24	0.0932
PromoDolNoEvid	165,875,376	273,711,194	987,109,943	24	0.3411
PromoDolOFF	307,388,437	569,220,252	2,458,214,152	24	0.1883

[590] **Datasources: National Sales Perspectives ™**, **National Disease and Therapeutic Index™**, and **IMS Integrated Promotional Services™**. The statements, findings, conclusions, views, and opinions contained and expressed in this dissertation are based in part on data obtained under license from the following IMS Health Incorporated information service(s): National Disease and Therapeutic Index™ (January 1998 through December 2009), Integrated Promotional Services ™ (January 2003 through December 2009), National Sales Perspectives ™ (January 1998 through December 2009). All Rights Reserved. The statements, findings, conclusions, views, and opinions contained and expressed herein are not necessarily those of IMS Health Incorporated or any of its affiliated or subsidiary entities.

[591] IMS dollars and units were negligible for Xyrem because the data source that collects this information was unavailable. As a result, Xyrem was excluded from testing for the values that include IMS dollars and units resulting in a sample size of 23 rather than 24.

Table G: Univariate Means[592,593]

Variable	Mean	Mean of low group	Mean of high group	N
AdjTotSettle	329,308,301	37,013,335	551,303,403	23
Units	1,974,437,051	102,784,286	3,414,169,948	23
TotalDollars	5,735,672,165	1,048,936,757	9,340,853,248	23
TotalDollarsOFF	4,386,585,808	502,431,224	8,623,845,355	23
UnitOFF	1,583,503,612	97,606,802	3,515,169,465	23
TotalDollarsNoEvid	2,640,816,205	300,054,572	4,786,514,369	23
UnitClin	1,054,261,089	46,012,800	2,154,168,313	23
AdjTotSettle	316,420,455	38,831,517	551,303,403	24
MedDollars	1,455,428,857	160,366,037	3,268,516,804	24
MedUnit	372,553,445	23,730,055	860,906,192	24
PromoDollars	406,193,389	12,563,537	871,392,306	24
Off-label Rate	0.63569	0.39034	0.84330	24
MedUnitOFF	304,292,693	8,311,083	654,089,140	24
MedDollarsNoEvid	624,984,417	51,755,757	1,198,213,078	24
MedDollarsOFF	1,117,391,746	59,901,696	2,174,881,796	24
MedUnitNoEvid	197,685,016	6,816,161	423,257,299	24
PromoDolNoEvid	165,875,376	10,208,065	383,809,611	24
D PromoDolOFF	307,388,437	12,367,580	720,417,636	24
NoEvidenceRate	0.45397	0.23227	0.71597	24

[592] **Datasources: IMS National Sales Perspectives™**, **IMS National Disease and Therapeutic Index™**, and **IMS Integrated Promotional Services™**. The statements, findings, conclusions, views, and opinions contained and expressed in this dissertation are based in part on data obtained under license from the following IMS Health Incorporated information service(s): National Disease and Therapeutic Index™ (January 1998 through December 2009), Integrated Promotional Services ™ (January 2003 through December 2009), National Sales Perspectives ™ (January 1998 through December 2009). All Rights Reserved. The statements, findings, conclusions, views, and opinions contained and expressed herein are not necessarily those of IMS Health Incorporated or any of its affiliated or subsidiary entities.

[593] IMS dollars and units were negligible for Xyrem because the data source that collects this information was unavailable. As a result, Xyrem was excluded from testing for the values that include IMS dollars and units resulting in a sample size of 23 rather than 24.

Table H: Total IMS and Medicaid Dollars and Units[594,595]

DrugName	medDol	medUnit	TotalDollars	Units	AdjTotSettle
Abilify	2,449,382,893	223,858,463	6,386,380,123	623,241,741	93,166,690
Actimmune	56,937,579	240,026	549,058,862	**1,689,191**	36,900,000
Actiq	223,213,204	13,121,957	2,067,149,510	124,950,414	175,656,582
Baycol	42,260,382	28,425,841	664,651,003	553,664,820	8,000,000
Bextra	339,335,395	116,959,398	2,776,405,848	1,117,890,943	2,300,000,000
Cardizem LA	33,312,386	17,330,392	627,207,560	311,142,180	24,600,000
Celexa	892,318,414	432,118,803	6,426,425,647	3,473,539,472	108,983,643
Evista	297,512,578	129,412,823	4,115,577,860	2,045,905,793	36,000,000
Gabitril	142,114,639	94,633,394	525,884,305	359,707,454	111,836,447
Genotropin	185,192,144	1,039,314	1,372,794,484	12,343,950	34,680,000
Intron A	80,431,384	7,362,972	1,494,742,244	12,898,860	206,093,387
Lexapro	1,592,045,870	665,915,457	15,328,738,670	6,955,299,820	194,445,117
Loprox	84,368,784	78,418,736	388,843,768	501,241,275	9,800,000
Neurontin	2,163,693,079	1,901,787,562	9,694,568,423	**9,729,710,751**	430,000,000
Oxycontin	2,038,040,020	563,608,902	11,092,018,849	3,674,719,725	634,515,475
Provigil	174,735,107	34,928,749	3,130,450,764	560,561,890	137,506,971
Seroquel	7,671,208,086	**2,097,393,979**	22,961,247,827	6,920,616,645	520,000,000

[594] **Total Dollars and Units data source: IMS National Sales Perspectives™**. The statements, findings, conclusions, views, and opinions contained and expressed in this dissertation are based in part on data obtained under license from the following IMS Health Incorporated information service(s): National Disease and Therapeutic Index™ (January 1998 through December 2009), Integrated Promotional Services ™ (January 2003 through December 2009), National Sales Perspectives ™ (January 1998 through December 2009). All Rights Reserved. The statements, findings, conclusions, views, and opinions contained and expressed herein are not necessarily those of IMS Health Incorporated or any of its affiliated or subsidiary entities.

[595] The values for IMS dollars and units for Xyrem were negligible because the data source did not track sales through the specialty pharmacies that sold Xyrem.

Serostim	623,722,136	2,830,077	779,153,422	4,023,208	704,000,000
Temodar	89,334,626	987,614	1,195,877,920	14,523,520	228,906,613
TOBI	506,400,514	51,196,253	1,749,125,881	182,441,685	72,500,000
Topamax	2,707,493,472	964,277,739	12,563,685,087	4,737,500,905	81,000,000
Trisenox	**723,354**	**32,574**	**128,373,386**	4,122,400	10,500,000
Xyrem	2,378,277	1,672,874	543	540	20,000,000
Zyprexa	**12,534,138,238**	1,513,728,791	**25,902,098,356**	3,490,315,539	1,415,000,000

Table I: Promotional Dollars and Allocated to Off-label and Non-evidence Based[596]

DrugName	PromoDollars	PromoDolOff	PromoDolNoEvid	AdjTotSettle
Abilify	951,957,701.19	593,898,512.16	244,779,887.77	93,166,690
Actimmune	**1,125,178**	1,125,178	1,125,178	36,900,000
Actiq	17,647,321	14,001,027	14,001,027	175,656,582
Baycol	0	0	0	8,000,000
Bextra	1,226,214,786	1,010,524,096	867,456,971	2,300,000,000
Cardizem LA	175,919,346	49,742,953	31,627,930	24,600,000
Celexa	230,191,498	187,069,441	78,942,444	108,983,643
Evista	320,812,999	181,039,472	140,564,515	36,000,000
Gabitril	49,499,348	47,993,290	46,944,782	111,836,447
Genotropin	4,235,922	**861,005**	812,390	34,680,000
Intron A	2,576,862	887,529	821,481	206,093,387
Lexapro	**3,171,773,141**	**2,458,214,152**	**987,109,943**	194,445,117
Loprox	22,614,547	8,935,905	4,912,723	9,800,000
Neurontin	134,493,787	132,832,313	124,664,497	430,000,000
Oxycontin	49,410,586	40,540,026	37,332,226	634,515,475
Provigil	309,419,648	252,506,778	230,396,949	137,506,971
Seroquel	1,026,308,989	842,270,927	483,283,428	520,000,000
Serostim	3,513,588	868,322	868,322	704,000,000

[596] **Datasources: IMS Integrated Promotional Services ™** and **IMS National Disease and Therapeutic Index™**. The statements, findings, conclusions, views, and opinions contained and expressed in this dissertation are based in part on data obtained under license from the following IMS Health Incorporated information service(s): National Disease and Therapeutic Index™ (January 1998 through December 2009), Integrated Promotional Services ™ (January 2003 through December 2009), National Sales Perspectives ™ (January 1998 through December 2009). All Rights Reserved. The statements, findings, conclusions, views, and opinions contained and expressed herein are not necessarily those of IMS Health Incorporated or any of its affiliated or subsidiary entities.

Temodar	4,179,684	3,558,041	662,787	228,906,613
TOBI	1,829,784	938,931	938,931	72,500,000
Topamax	592,187,526	424,210,317	214,237,865	81,000,000
Trisenox	1,967,423	965,928	**137,145**	10,500,000
Xyrem	4,725,738	2,727,987	2,727,987	20,000,000
Zyprexa	1,446,035,941	1,121,610,355	466,659,613	1,415,000,000

Table J: Estimated Total IMS Dollars and Units Allocated to Off-label and Non-evidence Based[597]

DrugName	TotDolOff	UnitOff	TotDolNoEvid	UnitNoEvid	AdjTotSettle
Abilify	3,984,275,402.59	388,822,257.79	1,642,150,074.36	160,256,115.61	93,166,690
Actimmune	549,058,862.00	1,689,191.00	549,058,862.00	1,689,191.00	36,900,000
Actiq	1,640,034,568.51	99,133,128.65	1,640,034,568.51	99,133,128.65	175,656,582
Baycol	**34,202,043.26**	28,490,844.13	27,089,383.33	22,565,885.67	8,000,000
Bextra	2,288,037,171.90	921,254,374.09	1,964,103,380.80	790,825,801.67	2,300,000,000
Cardizem LA	177,349,206.18	87,978,561.09	112,763,475.94	55,939,175.43	24,600,000
Celexa	5,222,555,409.56	2,822,837,041.35	2,203,894,376.97	1,191,224,256.07	108,983,643
Evista	2,322,480,840.66	1,154,534,592.15	1,803,244,279.23	896,415,532.05	36,000,000
Gabitril	509,883,851.09	348,763,064.74	498,744,428.46	341,143,644.82	111,836,447
Genotropin	279,037,823.81	2,509,063.80	263,282,589.61	2,367,395.24	34,680,000
Intron A	514,822,535.85	4,442,654.63	476,510,639.25	4,112,042.60	206,093,387
Lexapro	11,880,207,272.76	5,390,554,649.32	4,770,565,130.27	2,164,608,028.50	194,445,117
Loprox	153,647,609.05	198,060,326.02	84,471,372.02	108,888,303.47	9,800,000
Neurontin	9,574,806,195.29	**9,609,514,391.18**	8,986,054,502.88	**9,018,628,503.19**	430,000,000
Oxycontin	9,100,696,368.05	3,015,006,457.36	8,380,587,776.62	2,776,438,773.60	634,515,475
Provigil	2,554,653,663.48	457,455,361.50	2,330,964,792.06	417,399,961.82	137,506,971
Seroquel	18,843,829,403.12	5,679,609,418.67	**10,812,329,122.05**	3,258,881,462.24	520,000,000
Serostim	192,554,274.40	**994,266.18**	192,554,274.40	994,266.18	704,000,000
Temodar	1,018,015,370.56	12,363,441.41	189,634,395.87	2,303,043.56	228,906,613

[597] **Datasources: IMS National Sales Perspectives™ and IMS National Disease and Therapeutic Index™**. The statements, findings, conclusions, views, and opinions contained and expressed in this dissertation are based in part on data obtained under license from the following IMS Health Incorporated information service(s): National Disease and Therapeutic Index™ (January 1998 through December 2009), Integrated Promotional Services ™ (January 2003 through December 2009), National Sales Perspectives ™ (January 1998 through December 2009). All Rights Reserved. The statements, findings, conclusions, views, and opinions contained and expressed herein are not necessarily those of IMS Health Incorporated or any of its affiliated or subsidiary entities.

TOBI	897,542,214.35	93,617,683.97	897,542,214.35	93,617,683.97	72,500,000
Topamax	8,999,927,544.63	3,393,683,031.08	4,545,210,690.25	1,713,903,174.85	81,000,000
Trisenox	63,026,324.62	2,023,937.58	**8,948,658.09**	**287,364.45**	10,500,000
Xyrem	0.00	0.00	0.00	0.00	20,000,000
Zyprexa	**20,090,829,632.69**	2,707,245,331.81	8,359,033,732.17	1,126,382,307.93	1,415,000,000

Table K: Estimated Medicaid Dollars and Units Allocated to Off-label and Non-evidence Based[598]

DrugName	MedDolOff	MedUnitOff	MedDolNoEvid	MedUnitNoEvid	AdjTotSettle
Abilify	1,528,098,206.23	139,658,734.55	629,817,552.61	57,561,432.92	93,166,690
Actimmune	56,937,579.20	240,025.61	56,937,579.20	240,025.61	36,900,000
Actiq	177,092,836.56	10,410,694.72	177,092,836.56	10,410,694.72	175,656,582
Baycol	2,174,662.19	1,462,755.41	1,722,419.25	1,158,560.67	8,000,000
Bextra	279,646,435.24	96,386,286.84	240,054,888.81	82,740,190.66	2,300,000,000
Cardizem LA	9,419,410.11	4,900,341.62	5,989,118.58	3,115,771.23	24,600,000
Celexa	725,159,305.92	351,169,455.41	306,013,893.85	148,191,896.01	108,983,643
Evista	167,890,703.51	73,029,550.55	130,355,413.63	56,702,349.03	36,000,000
Gabitril	137,790,686.12	91,754,096.23	134,780,375.66	89,749,546.26	111,836,447
Genotropin	37,642,643.13	211,253.75	35,517,237.16	199,325.79	34,680,000
Intron A	27,702,360.97	2,535,971.52	25,640,815.65	2,347,250.41	206,093,387
Lexapro	1,233,880,707.95	516,103,367.91	495,471,850.37	207,244,257.11	194,445,117
Loprox	33,337,455.78	30,986,355.56	18,328,047.19	17,035,474.77	9,800,000
Neurontin	2,136,963,812.04	**1,878,293,755.39**	2,005,562,608.16	**1,762,798,088.45**	430,000,000
Oxycontin	1,672,155,778.28	462,425,601.60	1,539,843,514.09	425,835,363.32	634,515,475
Provigil	142,595,337.15	28,504,155.78	130,109,499.84	26,008,294.00	137,506,971
Seroquel	6,295,604,558.29	1,721,288,609.19	3,612,330,967.89	987,651,636.96	520,000,000
Serostim	154,142,123.90	699,404.47	154,142,123.90	699,404.47	704,000,000
Temodar	76,047,915.21	840,726.62	14,166,093.04	156,609.31	228,906,613
TOBI	259,853,132.20	26,270,721.08	259,853,132.20	26,270,721.08	72,500,000

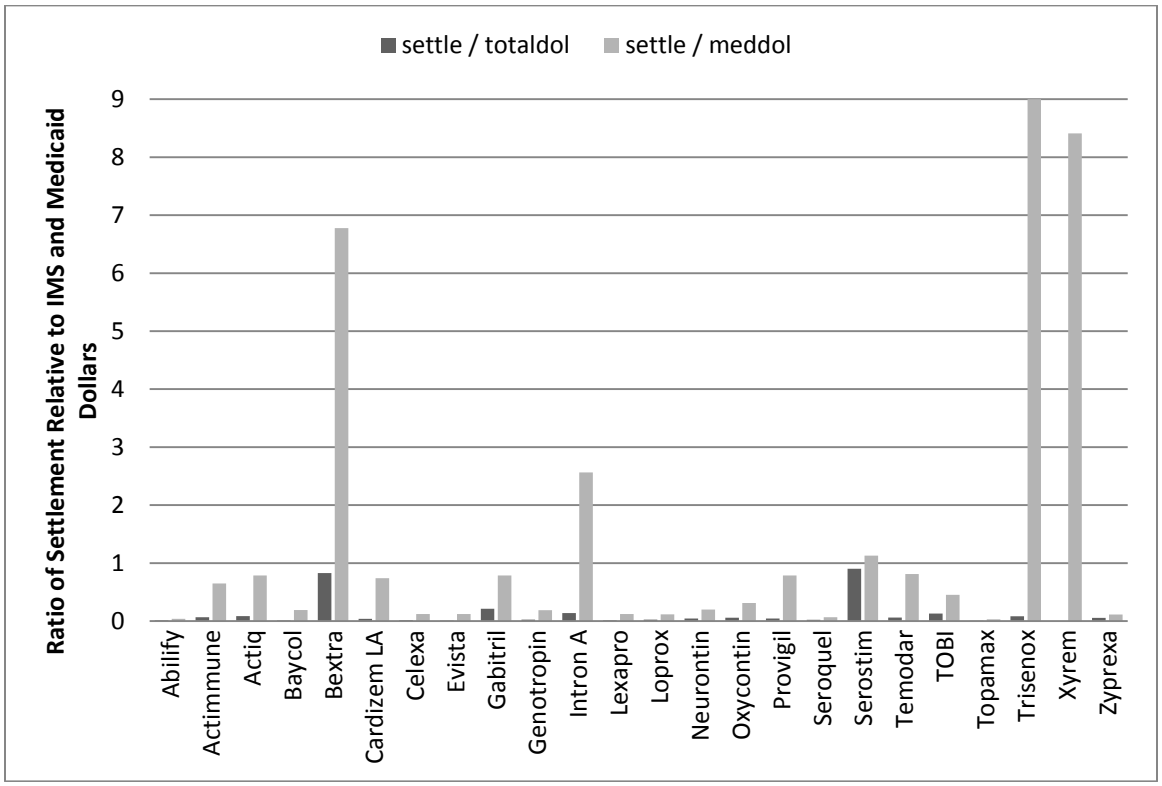
[598] **Datasources: IMS National Disease and Therapeutic Index™**. The statements, findings, conclusions, views, and opinions contained and expressed in this dissertation are based in part on data obtained under license from the following IMS Health Incorporated information service(s): National Disease and Therapeutic Index™ (January 1998 through December 2009), Integrated Promotional Services ™ (January 2003 through December 2009), National Sales Perspectives ™ (January 1998 through December 2009). All Rights Reserved. The statements, findings, conclusions, views, and opinions contained and expressed herein are not necessarily those of IMS Health Incorporated or any of its affiliated or subsidiary entities.

Topamax	1,939,498,237.12	690,755,118.96	979,499,899.01	348,850,314.13	81,000,000
Trisenox	**355,138.78**	**15,992.67**	**50,423.62**	**2,270.69**	10,500,000
Xyrem	1,372,887.88	965,685.74	1,372,887.88	965,685.74	20,000,000
Zyprexa	**9,722,039,985.73**	1,174,115,966.41	**4,044,972,839.45**	488,505,210.99	1,415,000,000

Table L: Mantel-Haenszel Categorization and Results

Off-Label use relative to all uses	< 100 million; 100 million plus	< 50 million; 50 million plus	< 0.7; 0.7 plus	0.0022
Non-evidence based use relative to all uses	< 100 million; 100 million plus	< 50 million; 50 million plus	< 0.4; 0.4 plus	0.4016
Medicaid units allocated to off-label use	< 100 million; 100 million plus	< 50 million; 50 million plus	< 35 million; 35 million plus	0.1727
Medicaid units allocated to non-evidence based use	< 100 million; 100 million plus	< 50 million; 50 million plus	< 50 million; 50 million plus	0.1727
IMS units allocated to off-label use	< 100 million; 100 million plus	< 50 million; 50 million plus	< 400 million; 400 million plus	0.0299
IMS units allocated to non-evidence based use	< 100 million; 100 million plus	< 50 million; 50 million plus	< 400 million; 400 million plus	0.0149
Medicaid dollars allocated to non-evidence based use	< 100 million; 100 million plus	< 50 million; 50 million plus	< 50 million; 50 million plus	0.0919
Medicaid dollars allocated to off-label use	< 100 million; 100 million plus	< 50 million; 50 million plus	< 155 million; 155 million plus	0.4465

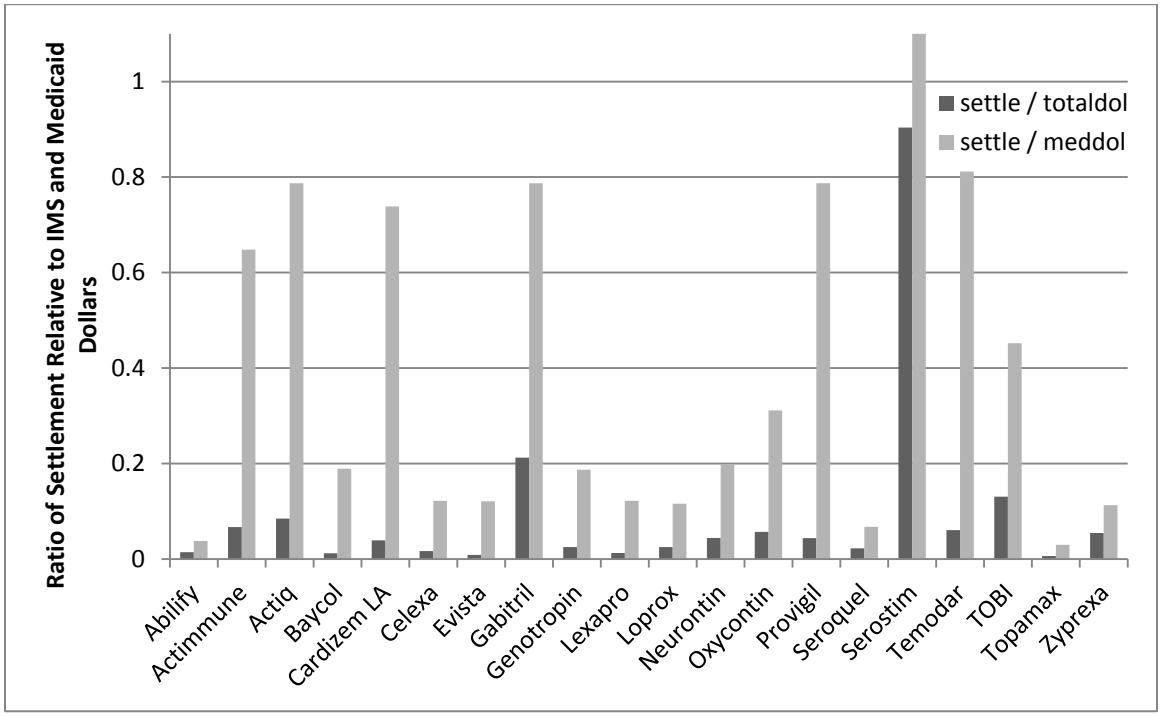
Figure IIa: Settlement Amount Relative to Total IMS and Medicaid Dollars[599,600]



[599] **Datasource: IMS National Sales Perspectives™.** The statements, findings, conclusions, views, and opinions contained and expressed in this dissertation are based in part on data obtained under license from the following IMS Health Incorporated information service(s): National Disease and Therapeutic Index™ (January 1998 through December 2009), Integrated Promotional Services ™ (January 2003 through December 2009), National Sales Perspectives ™ (January 1998 through December 2009). All Rights Reserved. The statements, findings, conclusions, views, and opinions contained and expressed herein are not necessarily those of IMS Health Incorporated or any of its affiliated or subsidiary entities.

[600] Trisenox is 14.515.

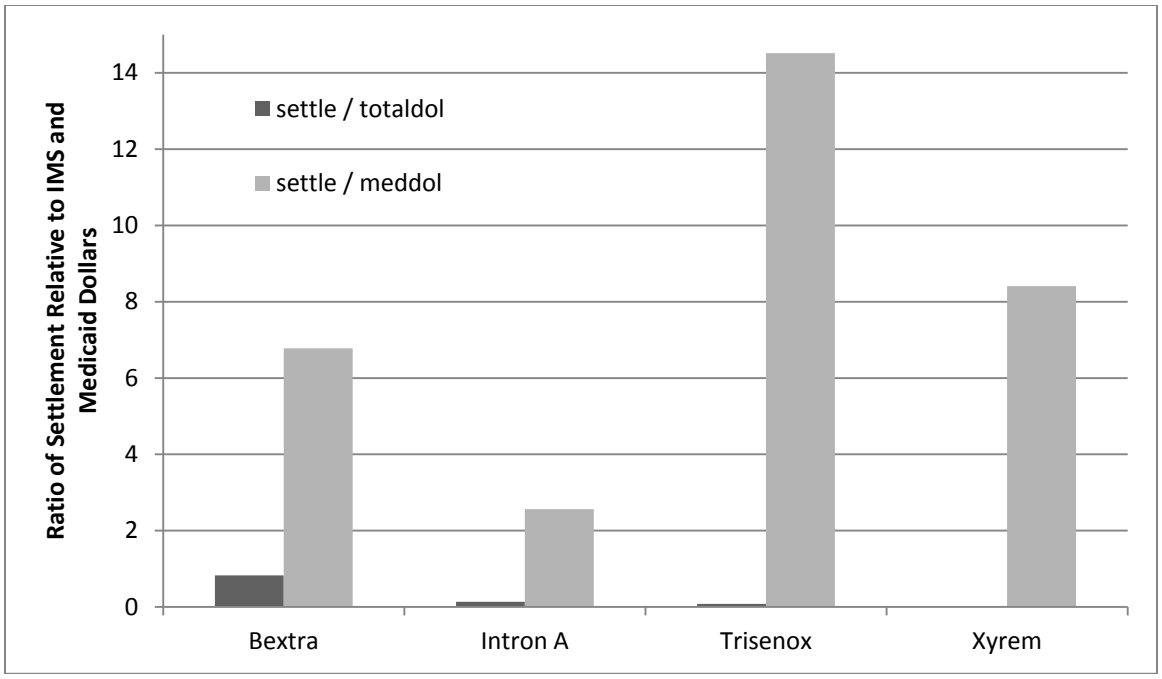
Figure IIb: Settlement Amount Relative to Total IMS Dollars and Medicaid Dollars[601,602]



[601] **Datasource: IMS National Sales Perspectives™**. The statements, findings, conclusions, views, and opinions contained and expressed in this dissertation are based in part on data obtained under license from the following IMS Health Incorporated information service(s): National Disease and Therapeutic Index™ (January 1998 through December 2009), Integrated Promotional Services ™ (January 2003 through December 2009), National Sales Perspectives ™ (January 1998 through December 2009). All Rights Reserved. The statements, findings, conclusions, views, and opinions contained and expressed herein are not necessarily those of IMS Health Incorporated or any of its affiliated or subsidiary entities.

[602] Bextra, Intron A, Trisenox, and Xyrem were removed for scaling purposes. All results are displayed in Figure IIa.

Figure IIc: Settlement Amount Relative to Total IMS Dollars and Medicaid Dollars[603,604]



[603] **Datasource: IMS National Sales Perspectives™**. The statements, findings, conclusions, views, and opinions contained and expressed in this dissertation are based in part on data obtained under license from the following IMS Health Incorporated information service(s): National Disease and Therapeutic Index™ (January 1998 through December 2009), Integrated Promotional Services ™ (January 2003 through December 2009), National Sales Perspectives ™ (January 1998 through December 2009). All Rights Reserved. The statements, findings, conclusions, views, and opinions contained and expressed herein are not necessarily those of IMS Health Incorporated or any of its affiliated or subsidiary entities.

[604] Bextra, Intron A, Trisenox, and Xyrem were removed for scaling purposes. All results are displayed in Figure IIa.

BIBLIOGRAPHY

Amended Complaint United States et al, ex rel. Frank Garcia & Christine Discolli v. Serono, Inc., No. 03-cv-11892, Oct. 10, 2003 (D. Mass.).

Amended Complaint, United States of America et al. *ex rel.* Laurie Simpson v. Bayer Healthcare d/b/a Bayer Healthcare Pharmaceuticals; Bayer Pharmaceuticals Corp.; Bayer Corp.; and Bayer A.G., No. 06-cv-4796, Mar. 31, 2008 (D. N.J.).

JOEL ANDROPHY, FEDERAL FALSE CLAIMS ACT AND QUI TAM LITIGATION § 506[1] (Law Journal Press-Litigation Series) (2008).

Bartrum T.E. & Bryant, Jr. L.E., *The Brave New World of Health Care Compliance Programs*, 6 Annals Health L. 51 (1997).

Brief of the United States as Amicus Curiae Supporting Plaintiffs 3, *In re* Pharm. Indus. Average Wholesale Price Litig., MDL No. 1456, 491 F. Supp.2d 20 (D. Mass. June 21, 2007) (Civil Action No. 01-CV-12257-PBS).

Bruera E, et al. *Randomized, double-blind, cross-over trial comparing safety and efficacy of oral controlled-release oxycodone with controlled-release morphine in patients with cancer pain*, 16 J Clin Oncol, 3222–3229 (1998).

Pamela H. Bucy, *Civil Prosecution of Health Care Fraud*, 30 Wake Forest L. Rev. 693, 721-22 (1995).

Centers for Medicare & Medicaid Services, *The 2008 Annual Report of the Boards of Trustees of the Federal Hospital Insurance and Federal Supplementary Medical Insurance Trust Funds* (2008).

Centers for Medicare and Medicaid Services, National Health Expenditure Projections, 2006–2016: Forecast Summary (with selected tables), http://www.cms.hhs.gov/NationalHealthExpendData/downloads/ proj2006.pdf (accessed Aug. 7, 2008).

Chen H., et al. *Off-label Use of Antidepressant, Anticonvulsant, and Antipsychotic Medications Among Georgia Medicaid Enrollees in 2001*, 67:6 J Clin Psychiatry 972 (June 2006).

Chen H., et al. *An epidemiological investigation of off-label anticonvulsant drug use in the Georgia Medicaid population*, 14 J Pharmacoepidemiol Drug Saf 629-638 (2005).

Chou R, et al. *Comparative efficacy and safety of long-acting oral opioids for chronic non-cancer pain*, J Pain Symptom Manage, 26(5): 1026-1048 (2003).

Complaint United States of America ex. rel. David Franklin v. Parke-Davis, division of Warner-Lambert Co., No. 96-cv-11651, Aug. 13 1996.

Complaint United States v. Eli Lilly Co.,No. 05-cv-1884, Dec. 21, 2005 (S.D. Indiana).

Complaint United States ex rel. Sandra Boucher et all v. Serono Labs., No. 05-cv-10722 (D. Maryland).

Complaint United States v. Schering Sales Corp. (a subsidiary of Schering-Plough Corp., No. 06-cr-10250 (D. Mass.).

Complaint, United States of America ex rel. Dr. Peter Rost v. Pfizer Inc. and Pharmacia Corp., No. 03-cv-11084, June 5, 2003 (D. Mass.).

Complaint United States of America ex. rel. Debbie Mulqueen, Lisa Altazan, Cynthia Hamilton, Jule Laib v. Medicis Pharmaceutical Corp., No. 04-cv-2389, August 20, 2004 (D. Kansas).

Complaint, United States of America et al. ex rel. Shelley Lauterbach v. Orphan Medical Inc., and Dr. Peter Gleason, No. 05-cv-00387, Jan. 24, 2005 (E.D.N.Y.).

Corrected First Amended Complaint, United States of America ex rel. James Marchese v. Cell Therapeutics, Inc., Medcomm Solutions, Envision Pharma, Inc. and Amerisourcebergen Corp., No. 06-cv-0168 (W.D. WA.).

Corporate Crime Reporter, The Top 100 False Claims Act Settlements, Taxpayers Against Fraud Education Fund at 3 (2003).

Dai C, et al., *National trends in cyclooxygenase-2 inhibitor use since market release: non-selective diffusion of a selectively cost-effective innovation*, 165(2) Arch Intern Med. 171-177 (2005).

DiMasi JA, Hansen RW, Grabowski HG. *The Price of Innovation: New Estimates of Drug Development Costs*. 22 J Health Econ, 151–185 (2003).

Eckstein A., The Pink Sheet, *Schering Corp. Accepts Federal Contract Ban Under Settlement*; 008 The FDC Reports, (July 30, 2004).

David Evans, Pfizer Broke the Law by Promoting Drugs for Unapproved Uses, Bloomberg (Nov. 9, 2009), http://preview.bloomberg.com/apps/news?pid=newsarchive_en10&sid=a4yV1nYxCGoA .

Everitt, B.S., The Analysis of Contingency Tables, London: Chapman and Hall, Ltd. (1977) at p. 40.

Fifth Amended Complaint, United States of America et al. *ex rel.* James Wetta v. AstraZeneca Corp., No. 04-cv-3479, Apr. 27, 2010 (E.D. Pa.).

Friedman (WLF II), 13 F.Supp. 2d at 58.

FDA Guidance for Industry, Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices U.S., Draft Guidance- September or October 2007.

FDA Alert: Information for Healthcare Professionals: valdecoxib (marketed as Bextra), dated April 7, 2005, available at www.fda.gov (last visited Aug. 22, 2012).

Henry F. Fradella, 44(2) Crim.L.Bull. 7.

Greene v. Sullivan, 731 F. Supp. 835, 837 (E.D.Tenn. 1990).

Guidance for Industry, Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices U.S., January 2009.

Guidance for Industry Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices, Draft Guidance, December 2011.

Hampton T. *Experts weigh in on promotion, prescription of off -label drugs*. 297 JAMA 683-84 (2007).

Hale ME, et al. *Efficacy and safety of controlled-release versus immediate-release oxycodone: randomized, double-blind evaluation in chronic back pain*. 15 Clin J Pain, 179–183 (1991).

Health Care Fraud, 57 United States Attorneys' Bulletin 1, 8–9 (Jan. 2009).
Pfizer Unit Pleads Guilty, Prosecutors Praise the Corporate Criminal, Not The Whistleblower, 21 Corporate Crime Reporter 15 (Apr. 3, 2007).

HHS & U.S. Dep't of Justice (DOJ), Health Care Fraud and Abuse Control Program Annual Report for FY 1998 (1998).

HHS, FDA Warning Letter transmitted to Micheal P. Bigelow, Attorney Eli Lilly and Company (Dec. 23, 1998).

IMS Health data as reported by the National Association of Chain Drug Stores, (May 7, 2007) http://www.nacds.org/wmspage.cfm?parm1=507.

Information, United States of America v. Biovail Pharmaceuticals Inc., No. 08-cr-10124, May 19, 2008 (D.Mass.).

Kaiser Family Foundation, Prescription Drug Trends May 2010.

Centers for Medicare & Medicaid Services, National Health Expenditure Accounts, Historical, http://www.cms.gov/NationalHealthExpendData/ accessed October 6, 2009.

Kaplan R, et al. Comparison of controlled-release and immediate-release oxycodone in cancer pain, 16 J Clin Oncol, 3230–3237 (1998).

Joan H. Krause, *A Conceptual Model of Health Care Fraud Enforcement*, 12 J.L. & Pol'y 55, 95 (2003).

Kesselheim AS, et al., *Whistleblower-initiated enforcement actions against health care fraud and abuse in the United States, 1996-2005*, 149 Ann Intern Med 342-9 (2008).

Kesselheim, AS, *et al*., *False Claims Act Prosecution Did Not Deter Off-label Drug Use in the Case of Neurontin*, 30(12) Health Affairs, 2318-27 (December 2011).

MICHEAL K. LOUCKS & CAROL C. LAM, PROSECUTING AND DEFENDING HEALTH CARE FRAUD CASES, 438 BUREAU OF NATIONAL AFFAIRS, INC. (June 2006).

MICHAEL K. LOUCKS & CAROL C. LAM, PROSECUTING AND DEFENDING HEALTH CARE FRAUD CASES 2007 SUPPLEMENT (59), (BNA books) (2007).

MARC C LEVY, OFF-LABEL COMMUNICATIONS: A GUIDE TO SALES & MARKETING COMPLIANCE 1, FOOD AND DRUG LAW INSTITUTE (2d Edition) (2009).

Mack A., *Examination of the Evidence for Off-Label Use of Gabapentin* 9(6) JMCP (Nov/Dec 2003).

Mantel, N. and Haenszel W., *Statistical aspects of the analysis of data from retrospective studies of disease*, J. Am. Pharma. Assoc., (1963).

MedAdNews, The magazine of pharmaceutical business and marketing, *The Top 500 Prescription Drugs by Worldwide Sales* (May 1998 to 2002).

Medicare Drug Focus Weekly Business Intelligence, *Schering Subsidiary Takes Fall For Criminal Charges Under DoJ Settlement*, 2:36 FDC Reports (Sept. 4, 2006).

Mello MM et al., *Shifting terrain in the regulation of off-label promotion of pharmaceuticals*, 360 N Engl J Med 1557-66 (2009).

Memorandum from Stephen R. Mason, Department of Health and Human Services, Food and Drug Administration to Henry Q. Waxman, Chairman Committee on Oversight and Government Reform, House of Representatives, dated December 21, 2007: attached Memorandum of Meeting April 13, 2007 Washington DC.

Memorandum from Henry Q. Waxman, Chairman Committee on Oversight and Government Reform, House of Representatives, to Andrew C. von Eschenbach, Commissioner, U.S. Food and Drug Administration (Nov. 30, 2007).

MICROMEDEX® Healthcare Series, Physician's Desk Reference (PDR).

MICROMEDEX® Healthcare Series, DRUGDEX® Evaluations.

Morita T, Hori A, Narimatatsu H, et al. Current status of development of anticancer agents in Japan, 87 *Int J Hematol* 484-89 *(*2008).

Niles S (2005) *Sales force effectiveness (the third in a series of articles that examine problems and solutions of detailing to physicians),* 24 Med Ad News 1.

Notices, Department of Health and Human Services, Office of Inspector General, *OIG Compliance Program Guidance for Pharmaceutical Manufacturers* 68 FR 23731 (May 5, 2003).

RJ Tenpas, Testimony to Committee on Oversight and Government Reform United States House of Representatives, *Allegations of Waste, Fraud, and Abuse in Pharmaceutical Pricing: Financial Impacts on Federal Health Programs and the Federal Taxpayer*, Associate Attorney General U.S. Department of Justice (February 9, 2007).

Rosenthal MB, Berndt ER, Donohue JM, Epstein AM, Frank RG (2003) Demand effects of recent changes in prescription drug promotion. Henry J Kaiser Family Foundation. Available: http*:*//www.kff.org/rxdrugs/6085-index.cfm. Accessed 23 March 2007.

Second Amended Complaint United States of America et al ex rel. Dr. Gary R. Spivack v. Johnson & Johnson, and Ortho-McNeil Pharmaceutical Inc., No. 04-cv-11886 (D. Mass.).

Staumbaugh JE, et al. *Double-blind, randomized comparison of the analgesic and pharmacokinetic profiles of controlled-and immediate-release oral oxycodone in cancer pain patients,* 41 J Clin Pharmacol, 500–506 (2001).

The Department of Health and Human Services and The Department of Justice Health Care Fraud and Abuse Control Program Annual Report for FY 2007, at 12 (Nov. 2008).

The Department of Health and Human Services and Department of Justice, Health Care Fraud and Abuse Control Program Annual Report for FY 2009 (May 2010).

The Department of Health and Human Services and Department of Justice, Health Care Fraud and Abuse Control Program Annual Report for FY 2011 (May 2012).

The Pink Sheet, *Serostim $704 Mil. Settlement Is Largest For Off-Label Marketing Case*, 67(43) FDC Reports 10 (Oct. 24, 2005).

The Pink Sheet. *Warner-Lambert's Neurontin Approved for Adjunctive Therapy in Epilepsy Patients*, 56(001) FDC Report, 11 (Jan. 3 1994).

The Medicaid Rebate Act and "Best Price" Provision, Taxpayers Against Fraud, http://www.drugfraudsettlement.com/Medicaid-and-States/Best-Price (available at Taf.org accessed 7/19/2008).

Orange Book, www.fda.gov/drugs.

Office of Inspector General, Corporate Integrity Agreements: General Information, http://oig.hhs.gov/fraud/cias.asp (last visited Oct. 22, 2008).

Pfizer Fact Sheet: Pfizer to pay $2.3 billion to resolve criminal and civil health care liability relating to fraudulent marketing and the payment of kickbacks, STOPMedicareFraud.gov, U.S. Department of Health and Human Services and U.S. Department of Justice, available at STOPMedicareFRAUD.gov (last visited Sept. 28, 2010).

Prescription Drugs: OxyContin Abuse and Diversion and Efforts to Address the Problem. Washington, DC: General Accounting Office; Publication No. GAO-04-110 (Dec. 2003).

Press Release, Two Johnson & Johnson Subsidiaries to Pay Over $81 Million to Resolve Allegations of Off-label Promotion of Topamax, Department of Justice (Apr. 29, 2010).

Press Release, Two Johnson & Johnson Subsidiaries to Pay Over $81 Million to Resolve Allegations of Off-label Promotion of Topamax, Department of Justice (Apr. 29, 2010).

Press Release, Department of Justice Office of Public Affairs, Novartis Vaccines & Diagnostics to Pay More Than $72 Million to Resolve False Claims Act Allegations Concerning TOBI (May 4, 2010).

Press Release, Department of Justice, Serono To Pay $704 Million For The Illegal Marketing Of AIDs Drug (Oct. 17, 2005).

Press Release, Department of Justice, Warner-Lambert to pay $430 Million to Resolve Criminal & Civil Health Care Liability Relating to Off-Label Promotion (May 13, 2004).

Press Release, U.S. Attorney's Office Western District Of Virginia, The Purdue Frederick Company, Inc. and Top Executives Plead Guilty to Misbranding Oxycontin; will Pay over $600 Million, (May 10, 2007).

Press Release, Department of Justice, Schering-Plough To Pay $345 Million To Resolve Criminal And Civil Liabilities For Illegal Marketing Of Claritin (July 30, 2004).

Press Release, Michael J. Sullivan, Department of Justice, Schering To Pay $435 Million For The Improper Marketing Of Drugs And Medicaid Fraud (Aug. 29, 2006).

Press Release, Department of Justice Eli Lilly and Company To Pay U.S. $36 Million Relating To Off-Label Promotion (Dec. 21, 2005).

Press Release, Dep't of Justice, Serono to Pay $704 Million For The Illegal Marketing of AIDS Drug (Oct. 17, 2005).

Press Release, Biopharmaceutical Firm Intermune to Pay U.S. Over $36 Million for Illegal Promotion and Marketing of Drug Actimmune, Department of Justice (Oct. 26, 2006).

Press Release, Bristol-Myers Squibb to Pay More Than $515 Million to Resolve Allegations of Illegal Drug Marketing and Pricing, Department of Justice (Sept. 28, 2007).

Press Release, Otsuka to Pay More than $4 Million to Resolve off-label Marketing Allegations Involving Abilify, Department of Justice (Mar. 27, 2008).

Press Release, Cell Therapeutics, Inc. to Pay United States $10.5 Million to Resolve Claims for Illegal Marketing of Cancer Drug, Department of Justice (Apr. 17, 2007).

Press Release, Medicis Pharmaceutical To Pay U.S. $9.8 Million to Resolve False Claims Allegations, Department of Justice (May 8, 2007).

Press Release, New Jersey Company Agrees To Plead Guilty To Kickbacks And Conspiracy Charges And Pay More Than $22 Million Dollars In Criminal Fines, Department of Justice, United States Attorney Michael J. Sullivan District of Massachusetts (May 16, 2008).

Press Release, Biovail Enters Guilty Plea, Signs Civil Agreement, Reuters (Sept. 14, 2009).

Press Release, Biopharmaceutical Company, Cephalon, to Pay $425 Million & Enter Plea to Resolve Allegations of Off-Label Marketing, Department of Justice (Sept. 29, 2008).

Press Release, Department of Justice, Eli Lilly and Company Agrees to Pay $1.415 Billion to Resolve Allegations of Off-label Promotion of Zyprexa: $515 Million Criminal Fine Is Largest Individual Corporate Criminal Fine in History; Civil Settlement up to $800 Million (Jan. 15, 2009).

Press Release, Justice Department Announces Largest Health Care Fraud Settlement in its History, Department of Justice, U.S. Department of Health and Human Services (Sept. 2, 2009).

Press Release, Drug Maker Forest Pleads Guilty; To Pay More Than $313 Million To Resolve Criminal Charges and False Claims Act Allegations, Department of Justice, Office of Public Affairs (Sept. 15, 2010).

Press Release, Pharmaceutical Giant AstraZeneca to Pay $520 Million for Off-label Drug Marketing, Department of Justice, Office of Public Affairs (Apr. 27, 2010).

Press Release, Novartis Vaccines & Diagnostics to Pay More Than $72 million to Resolve False Claims Act Allegations Concerning TOBI, Department of Justice, Office of Public Affairs (May 4, 2010).

Press Release, Two Johnson & Johnson Subsidiaries to Pay Over $81 Million to Resolve Allegations of Off-label Promotion of Topamax, Department of Justice (Apr. 29, 2010).

Press Release, Merck to Pay more than $650 million to resolve claims of fraudulent price reporting and kickbacks, Department of Justice, February 7th, 2008
Second Amended Complaint, United States *ex rel*. Joseph Faltaous v. Eli Lilly & Co., ¶ 12 (06-cv-2909) (E.D. Pa. July, 10 2008)

PR Newswire, United Business Media, Justice Department Recovers $2.4 Billion in False Claims Cases in Fiscal Year 2009; More Than $24 Billion Since 1986 (2009).

Qureshi ZP, et al., *Pharmaceutical Fraud and Abuse in the United States, 1996-2010*, 171(16) Arch Intern Med, 1503-505 (Sept 12, 2011).

Qureshi ZP, et al., *Enforcement Actions Involving Medicaid Fraud and Abuse, 1996-2009*, 171(16) Arch Intern Med, 785-87 (Apr 25, 2011).

Radley D, Finkelstein S, Stafford RS. *Off-label prescribing among office-based physicians* 166 Arch Intern Med. 1021–6 (2006).

Janet Rae-Dupree, *Putting a Mistake Behind It, Genentech Pays a $50 Million Fine*, Business Week (Apr. 15, 1999), available at http://www.businessweek.com/bwdaily/dnflash/apr1999/nf90415c.htm.

Senate Committee on Labor and Human Resources, Testimony of
Deputy Commissioner For Policy, Food And Drug Administration William B. Schultz, Hearing on Unapproved Prescription Drugs and Medical Devices, l05th Cong. (Feb. 22, 1996).

Stafford, RS, *Regulating Off-Label Drug Use – Rethinking the Role of the FDA*, 358(14) New Eng. J. Med. 1427 (2008).

SIEGEL, S. NONPARAMETRIC STATISTICS FOR THE BEHAVIORAL SCIENCES, NEW YORK: MCGRAW AND HILL (1956).

SIEGEL, 1956; NORMAN G.R. AND STREINER, D.L. PDQ STATISTICS. TORONTO AND PHILADELPHIA: B.C. DECKER, INC. (1986).

Taxpayer's Against Fraud, www.taf.org.

The Enforcement Story, Office of Criminal Investigations, FY 2006 Report.

Third Amended Complaint, United States of America et al. *ex rel.* John Kopchinski v. Pfizer and Pharmacia Corp., No. 05-cv-12115-RCL, Dec. 22, 2008 (D. Mass).

Third Amended Complaint, United States *ex rel.* Radcliffe v. Purdue Pharma, No. 05-cv-00089, June 5, 2007 (W.D. Va.).

U.S. *ex rel*. Franklin v. Parke-Davis, 147 F. Supp. 2d 39 (D. Mass. 2001)
U.S. *ex rel*. Hess v. Sanofi-Synthelabo, Inc., 2006 WL 1064127 (E.D. Mo. April 21, 2006).

U.S. *ex rel*. Lamers v. City of Green Bay, 168 F.3d 1013, 1018 (7th Cir. 1999).

U.S. *ex rel.* Wilkins v. N. Am. Constr. Corp. 173 F.Supp.2d 601, 626 (S.D. Tex. 2001).

United States of America v. Scott Harkonen, No. 08-cr-0164, Mar. 18, 2008 (N.D. CA.).

United States of America et al. *ex rel*. Dr. Gary R. Spivack v. Johnson & Johnson, and Ortho-

McNeil Pharmaceutical Inc., No. 04-cv-11886, Dec. 7, 2007 (D. Mass.).

United States of America, *ex. rel*. Robert Lally, Courtney Davis and William Manos v. Novartis Vaccines and Diagnostics, Inc.; and Express Scripts, Inc. (fdba Priority Healthcare Corp.), No. 06-cv-6303, Oct. 6, 2006 (N.D. CA).

U.S. Department of Health and Human Services: Office of Inspector General, *The Effect of Exclusion From Participation in Federal Health Care Programs* (Sept. 1999).

U.S. Dep't of Health & Human Servs. & Dep't of Justice, *Annual Report of the Department of Health and Human Services and the Department of Justice, Health Care Fraud and Abuse Control Programs FY 1999* (2000).

U.S. Dep't of Health & Human Servs. & Dep't of Justice, *Annual Report of the Department of Health and Human Services and the Department of Justice, Health Care Fraud and Abuse Control Programs FY 2006* (2008), available at http://www.oig.hhs.gov/publications/docs/hcfac/hcfacreport2006.pdf

U.S. Department of Health & Human Services, Office of Inspector General, *Entities by Classification*: *HHS-OIG Fraud Prevention & Detection – Classification Details*, http://exclusions.oig.hhs.gov/ClassificationDetails.aspx?id=46 (last visited Oct. 29, 2008).

U.S. Dep't of Health & Human Servs. & Dep't of Justice, Health Care Fraud And Abuse Control Program Annual Report For FY 1998 (1998), http://www.usdoj.gov/dag/pubdoc/98hipaa_ar.htm#a (last visited July 15, 2008).

Washington Legal Foundation v. Leavitt, 477 F.Supp. 2d 202, 333 (D.D.C. 2007).

Zee Van, *The Promotion and Marketing of OxyContin: Commercial Triumph, Public Health Tragedy*, 99 Am J Public Health 221–227 (2009).

21 U.S.C § 321.

21 U.S.C. § 360.

21 U.S.C. §§ 355.
21 U.S.C. § 331.

31 U.S.C. § 1396.

31 U.S.C. § 3729.

42 C.F.R. § 1001.2.

42 U.S.C. § 1395 (2008).

42 U.S.C. § 1396 (2006).

42 U.S.C. § 1320.

Mayo Chronicles Medicare Regs: It's 132,720 Pages of Red Tape, Modern Healthcare, Mar. 15, 1999, at 64.

68 Fed. Reg. 50428, 50429 (Aug. 20, 2003).

Section 1395(x)(s)(2) (2006).

21 C.F.R. § 201.5.

21 C.F.R. § 201.128.

21 C.F.R. § 99.101.

21 C.F.R. § 99.3.

21 C.F.R. §99.1.

42 U.S.C. § 1320a-7b(b)(1)-(2) (2006).

42 U.S.C. § 1320a-7b(b).

Issuance of Final Rules Implementing the Anti-Kickback Statute, 56 Fed. Reg. 35952 (July 29, 1991) (to be codified at 43 C.F.R. pt. 1001).

S. Rep. No. 109, 100th Cong., 1st Sess. 1-2 (1987), reprinted in 1987 U.S.C.C.A.N. 682, 684.

Special Advisory Bulletin, Medicare-Medicaid Anti-Fraud and Abuse Amendments, Pub.L. 95-142.