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January 14, 2015

2014 YEAR-END FDA AND HEALTH CARE COMPLIANCE AND ENFORCEMENT UPDATE - DRUGS AND DEVICES

To Our Clients and Friends:

Pharmaceutical and medical device manufacturers are among the most highly regulated enterprises in the United States, and 2014 demonstrated that the regulatory landscape continues to be a minefield for these companies. This past year, the Department of Justice ("DOJ") and the U.S. Food and Drug Administration ("FDA") sustained their extensive enforcement efforts against businesses and executives alike, collecting hundreds of millions of dollars in civil recoveries and securing corporate criminal convictions for a broad range of conduct. The FDA also issued significant new rules and guidance in several areas, such as online promotional activity, current good manufacturing practices ("cGMP") compliance, drug development, and numerous issues affecting device makers, including an important update to the 510(k) clearance process. All of this activity in 2014 pointed to what promises to be an even busier regulatory and enforcement year in 2015.

Because so many of our clients now have an interest in the regulation of both drugs and devices, this update covers them together. It focuses first on notable government enforcement efforts against drug and device companies in 2014, including False Claims Act ("FCA") and Federal Food, Drug, and Cosmetic Act ("FDCA") cases. With the potential enforcement consequences in mind, the update then discusses key regulatory developments this past year in areas important to drug and device companies: promotional issues, including new online advertising rules and related case law; cGMP compliance; rules and case law relating to devices specifically; the Anti-Kickback Statute; and drug development and clinical trials.

I. DOJ Enforcement in the Pharmaceutical and Medical Device Industries

As in recent years, in 2014, the DOJ closely monitored--and frequently targeted for enforcement--companies in the drug and device industries. The DOJ collected more than $350 million in fines and penalties from pharmaceutical and medical device companies through civil actions brought under the FCA, alleging improper kickbacks, off-label promotion, false or misleading advertising, and improper billing. In addition, the DOJ brought several enforcement actions this year directly under the FDCA, targeting companies for alleged off-label promotion, misbranding, or product adulteration. Finally, the DOJ's focus on industry sales practices was not limited to U.S. territory; rather, the government continued to target companies in the drug and device industries for alleged corruption overseas, as illustrated by two recent Foreign Corrupt Practices Act ("FCPA") enforcement actions.

A. Civil Actions / False Claims Act

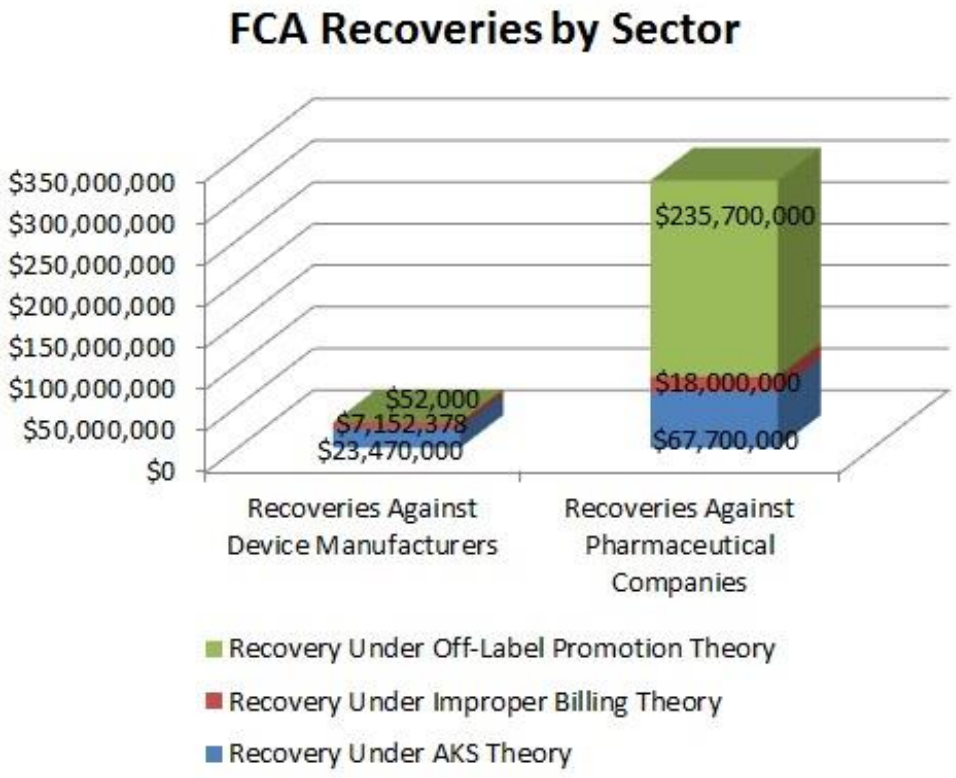
It has been an "extraordinary year for civil fraud recoveries,"[1] with the DOJ announcing a record $5.69 billion in settlements and judgments stemming from FCA cases during Fiscal Year 2014[2] and promising to "continue to enforce the law aggressively."[3] The FCA is the government's primary weapon for prosecuting fraud on the federal government, and companies found liable under the FCA must pay $5,500 to $11,000 per false claim in civil penalties, plus three times the government's damages. Meanwhile, whistleblowers--known as *qui tam* "relators" under the FCA--may bring suits on the government's behalf and are entitled to as much as 30% of the civil penalty recovered. This is a powerful incentive, given that government recoveries can extend into the millions (or even billions) of dollars.

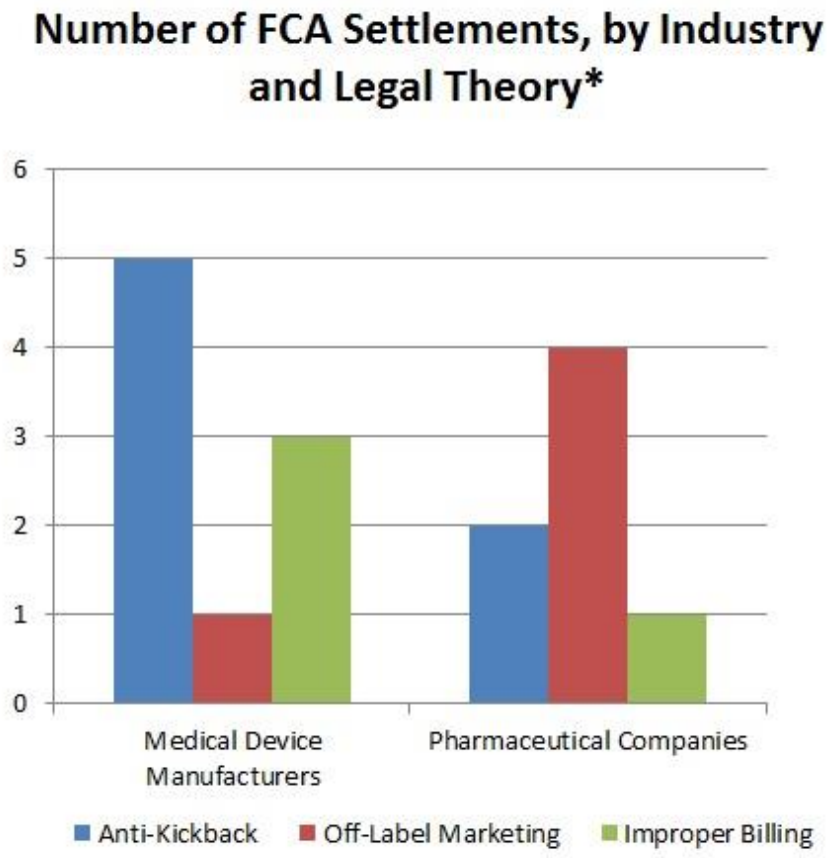
Since the late 1990s, cases involving allegations of health care fraud have made up the lion's share of FCA investigations, and 2014 was no different. Exactly 500 new FCA matters involving investigation of some form of health care fraud were initiated in 2014--the second-highest total ever for this category (and close behind the 529 new health care-related cases initiated in 2013).[4] As in past years, relators have continued to drive this activity, with 469 of the 500 new health care FCA matters coming from new *qui tam* filings alleging some form of health care fraud.[5]

It is an astonishing fact--and one revealing of today's FCA landscape--that in 2014 the DOJ enjoyed its lowest amount of health care-related FCA recoveries in five years, but still recovered **$2.3 billion** in such cases. Coming off of the $2.2 billion global settlement with Johnson & Johnson at the end of 2013, the DOJ also saw a downtick in the amount of FCA recoveries specifically from drug and device companies in the 2014 calendar year. But even without the billion-dollar settlements with pharmaceutical companies that occurred periodically over the past five years, the DOJ continued its aggressive pursuit of cases against drug and device companies. During 2014, the DOJ recovered a total of $321.4 million through six separate FCA enforcement actions against pharmaceutical companies (including instances in which the DOJ settled multiple claims against the same company at the same time),[6] and slightly more than $31 million through eight separate FCA enforcement actions against medical device companies.[7] All but two of the total of fourteen stemmed from allegations made by *qui tam* relators.[8]

Both drug and device companies may engage in sales and marketing activities that the DOJ views as a violation of the FCA. For instance, a company may be exposed to liability under the FCA if it promotes a drug or device for a use or uses not approved by the FDA. In such cases, the government typically alleges that the company "causes" physicians to submit false claims for drugs or devices that are not eligible for reimbursement by government payors because the use is neither approved nor medically accepted--or is not reasonable and necessary. Another prominent allegation is that the company provides improper financial or other valuable incentives to physicians to prescribe its drug or use its device over those of competitors, in possible violation of the Anti-Kickback Statute ("AKS"). Under the Patient Protection and Affordable Care Act of 2010 ("PPACA"), a claim for payment by a federal health program that "includes items or services resulting from" an AKS violation "constitutes a false or fraudulent claim" for FCA purposes.[9] In 2014, the DOJ continued to pursue

liability under each of these theories, among other allegations that drug and device companies "caused" health care providers to submit false claims.





* *Where settlements alleged multiple legal theories, each theory is counted.*

Even after years of eye-popping civil and criminal settlements based on off-label promotion, the DOJ continues to advance and settle such cases. Four of the fourteen FCA actions resolved by pharmaceutical and medical device companies (three against drug companies and one against a device company) in 2014 involved theories of off-label promotion. Those actions resulted in approximately $236.2 million in total civil fines. One drug company and its subsidiary paid the bulk of these off-label civil fines in February 2014, after agreeing to pay $192.7 million to resolve criminal and civil claims that stemmed from the companies' marketing of a prescription drug for uses not approved as safe and effective by the FDA. Of this figure, the civil false claims component totaled $171.9 million. As part of the settlement, the subsidiary agreed to enter into a Corporate Integrity Agreement ("CIA") with the U.S. Department of Health and Human Services Office of Inspector General ("HHS OIG") that requires the company to implement measures designed to avoid or promptly detect conduct similar to that which gave rise to the settlement. Notably, the CIA requires the company to implement an internal risk assessment and mitigation program mandating numerous internal and external reviews of promotional and other practices, and requires key executives and individual board members to sign compliance certifications.

Six of the fourteen FCA actions in the industries in 2014 (two against drug companies and four against device companies) relied on allegations that the defendants paid unlawful kickbacks in violation of the AKS,[10] resulting in approximately $91 million in total recoveries. In connection with the government's October settlement with a device manufacturer, Acting Deputy AAG August Flentje of the DOJ's Civil Division stressed that the settlement "demonstrates the [DOJ's] commitment to protect patients, and the taxpayers who fund their care, by ensuring that medical decisions are based on the patients' medical needs rather than the financial interests of others."[11]

The remaining four settlements (three with device companies and one with a drug company) involved a variety of theories. For example, in February, a device manufacturer paid $5.25 million to settle allegations that it caused physicians to overbill for procedures involving its device by using an inflated reimbursement code.[12] Such cases demonstrate that, in addition to the intense focus on misbranding (through off-label promotion), the government also continues to scrutinize drug and device makers' other promotional practices.

The past year also saw several notable court decisions shaping the contours of potential FCA theories against drug and device companies. For instance, in *United States ex rel. Rostholder v. Omnicare, Inc.*, the Fourth Circuit confirmed that violations of the FDCA's cGMP provisions do not, on their own, provide a basis for concluding that claims for government payment for associated drugs or devices were false or fraudulent.[13] Similarly, in *United States ex rel. Simpson v. Bayer Corp.*, the U.S. District Court for the District of New Jersey dismissed FCA claims alleging off-label promotion on the reasoning that FDCA violations, without more, cannot serve as a basis for FCA liability.[14] These cases are discussed in greater detail in the cGMP and Promotional Issues sections below.

Drug and device companies were also involved in cases clarifying or construing the FCA's procedural requirements, such as the first-to-file bar, which prohibits follow-on relators from renewing FCA claims that previous plaintiffs already asserted. For example, many in the industry were no doubt relieved to see the First Circuit, in *United States ex rel. Ven-A-Care of the Florida Keys, Inc. v. Baxter Healthcare Corp*., affirm that copycat relators cannot bring allegations of Average Wholesale Price reporting violations by drug companies, even if the allegations are more detailed than those in previous complaints.[15] The *Baxter* case, and other court decisions construing FCA requirements in drug and device cases, are analyzed in more detail in our 2014 False Claims Act Year-End Update.

B. FDCA Enforcement Actions

The FDCA prohibits, among other things, the "introduction or delivery for introduction into interstate commerce" of any drug or medical device that is adulterated or misbranded.[16] FDCA enforcement often falls into three categories of charges: marketing a product that has not been approved by the FDA for any use; marketing a product for a specific use that has not been FDA-approved; and marketing adulterated products, such as products not manufactured in conformance with the cGMP regulations. All three theories were featured in FDCA enforcement actions pursued or resolved by the DOJ in 2014.

1. Marketing Without Approval

In December, OtisMed Corporation and its CEO pled guilty to charges of distributing its knee replacement surgery cutting guide device without FDA approval.[17] The criminal information asserted that OtisMed falsely told physicians and other potential customers that the device was exempt from premarket review requirements. When the company eventually submitted a premarket notification for clearance of the device, the FDA refused to clear the device, but the company continued to market it anyway. In connection with the guilty plea, OtisMed paid $34.4 million in fines and $5.16 million in criminal forfeiture, on top of $40 million in payments to resolve alleged FCA liability.

2. Misbranding Violations

In the most high-profile FDCA enforcement action of 2014, Endo Pharmaceuticals pled guilty in February to misbranding its drug Lidoderm, and entered into a deferred prosecution agreement ("DPA") to resolve charges that it promoted the drug for unapproved uses.[18] Specifically, Endo allegedly promoted Lidoderm for a variety of types of pain, even though the drug was only approved for relief of pain associated with post-herpetic neuralgia. In addition to the DPA, Endo paid $20.8 million in criminal forfeiture; as noted above, it also paid $171.9 million to resolve civil FCA allegations.

And in October, the DOJ filed for an injunction against a manufacturer of low-level laser devices and its owner, on the basis of misbranding violations.[19] The suit alleges that the company repeatedly promoted its devices, which were cleared only for temporary pain relief, for "hundreds" of conditions including cancer, AIDS, and venereal disease. According to allegations in the government's complaint, not only is there no clinical support that such treatment is effective, but use of the laser on the skin can be harmful. The FDA allegedly warned the manufacturer repeatedly of its violations.

3. cGMPs

The FDA generally enforces cGMP regulations through inspections, FDA Form 483 observations, untitled letters, warning letters, civil injunctions, consent decrees, and civil fines. The same cGMP violations also can expose a company to criminal liability under the FDCA, particularly in egregious cases in which a company ignores repeated warnings. Manufacturers have been reminded in recent years of this enforcement route for cGMP issues, with high-profile criminal actions involving major drug companies. In 2014, the DOJ continued its active pursuit of entities that manufactured products that were allegedly adulterated because of cGMP violations.

In October, the DOJ filed a complaint for a permanent injunction against a device manufacturer and its owner, primarily alleging that the defendants violated the FDCA by manufacturing and distributing adulterated gels used in ultrasound scans.[20] The complaint alleges that FDA inspections found numerous deviations from cGMP requirements, including lack of process validation, improper monitoring of water systems, and failure to routinely sanitize water systems. Despite numerous FDA warnings, the gel manufacturer allegedly failed to bring its manufacturing processes into cGMP compliance, and one hospital discovered infections in patients on whom the gel had been used. The

government further asserts that the manufacturer failed to seek premarket approval or clearance for new products it marketed and seeks to enjoin manufacturing and distributing of devices until the company achieves FDCA compliance.

Manufacturing problems at pharmaceutical compounders also have been a high-profile concern in recent years, particularly in light of the 2012 meningitis outbreak traced to New England Compounding Center, whose principals were charged in 2014 with murder, racketeering, and FDCA violations. Other compounders were swept up in the increased scrutiny of this sector as well. In December, Main Street Family Pharmacy, LLC and a co-owner each pled guilty to a misdemeanor criminal violation of the FDCA.[21] The complaint alleged that the pharmacy did not obtain patient-specific prescriptions for its compounded preparations, and thus the pharmacy was not entitled to exemptions from the FDCA's cGMP, new drug, and "adequate directions for use" provisions. The pharmacy's co-owner was sentenced to twelve months of probation under the terms of the plea deal, and both the pharmacy and co-owner were ordered to pay a $25,000 fine.

C. FCPA Investigations of Pharmaceutical Manufacturers and Medical Device Companies

This past year, the DOJ continued to target drug and device companies for investigations relating to the FCPA's anti-bribery and accounting provisions. For a more comprehensive description of these actions, please see Gibson Dunn's FCPA 2014 Mid-Year and Year-End Updates.

1. Medical Device Manufacturer Settlement

In November, a California-based device manufacturer entered into a Non-Prosecution Agreement with the DOJ and a settlement agreement with the SEC.[22] The manufacturer allegedly paid bribes, via consultants, to foreign government officials in Russia, Thailand, and Vietnam to secure government contracts, and failed to adequately detect the improper behavior and prevent its consultants from making these payments. On that basis, the DOJ and SEC required the manufacturer to pay more than $55 million in criminal and civil penalties and disgorgement to resolve the potential FCPA charges. As is the case with most FCPA resolutions, the manufacturer will have to improve its anti-corruption compliance program and report its progress to the DOJ and SEC.

2. Scientific Instrument Manufacturer Settlement

In December, a Massachusetts-based manufacturer of scientific instruments (including infrared spectrometers and microscopes) entered into a settlement agreement with the SEC to resolve allegations that the company improperly provided travel and entertainment benefits to employees of Chinese state-owned enterprises.[23] The SEC alleged that the instrument manufacturer arranged for these officials to visit countries as far away as Europe, and in some cases paid them in cash to help secure government contracts. As a result of the instrument manufacturer's voluntary disclosure of the violations and its cooperation with the SEC's investigation, the manufacturer entered into a relatively small settlement (by FCPA standards) of less than $2.5 million, including penalties and disgorgement.

3. GlaxoSmithKline ("GSK") Investigation

In May, China's Ministry of Public Security announced the completion of its investigation of the Chinese subsidiary of GSK, stating that it had referred the case to state prosecutors. Police allege that a former executive of the company (a British national) ordered subordinates to pay £320 million in bribes to government health care officials throughout China over several years to boost the company's sales and delay the adoption of competing generic drugs. Ultimately, the company was fined a record ¥3 billion (approximately $489 million) by the Chinese government.

As of July 28, 2014, both the FBI and the SEC have reportedly been interviewing current and former company employees in connection with the bribery allegations made against GSK in China.[24]

II. Promotional Issues

In many ways, 2014 epitomized how the government's approach to drug and device promotional issues has evolved in response to legal and technological advances. This past year, the FDA's administrative enforcement activities and regulatory guidance increasingly focused on the electronic technologies that are a major part of modern promotion and advertising. Yet again, the DOJ and state authorities secured huge monetary recoveries from enforcement actions based on off-label promotion allegations. And the impact of *Sorrell v. IMS Health, Inc.*[25] and *United States v. Caronia*,[26] two landmark decisions recognizing certain First Amendment protections for pharmaceutical marketing, continued their increasing influence on the regulatory landscape and contemporary litigation of promotional issues. In sum, 2014 showed us much of what will be in store for drug and device companies in 2015 and beyond with respect to promotional issues. We address the following developments below: the FDA's administrative enforcement efforts with respect to advertising and promotion; federal and state enforcement of the FDCA's misbranding provisions and state advertising statutes; the FDA's new and updated draft regulatory guidance; and notable developments in case law addressing promotional issues.

A. FDA Enforcement Activity – Advertising and Promotion

In 2014, FDA warning letters and untitled letters for advertising and promotion declined to the lowest number in five years, but the year saw an uptick specifically in response to electronic promotions. During the past year, the FDA's Office of Prescription Drug Promotion ("OPDP") issued just ten letters, including only one warning letter and nine untitled letters,[27] representing more than a 50% decline from 2013, and an 80% decline from 2010.[28] But the percentage of letters citing electronic communications such as social media, email, and online postings, increased from 2013 and comprised about a third of the relatively small number of OPDP letters in 2014.[29] The FDA issued untitled letters to three drug manufacturers relating to promotions made through email, Google sponsored links, and a Facebook posting.[30] The FDA's focus on electronic promotions is sure to grow in 2015, as companies expand their online marketing efforts and attempt to capitalize on the popularity of social media.

Although the FDA has stated that 2014's smaller figures do not reflect an official change in enforcement policy,[31] it is interesting to juxtapose the FDA's trend with two key developments in

2012: (1) the zenith of the government's multibillion dollar civil recoveries and accompanying criminal pleas in cases involving off-label promotion conduct; and (2) the Second Circuit's recognition in *Caronia* that truthful, non-misleading off-label promotion can be protected speech under the First Amendment. In 2010 and 2011, the FDA issued eighteen warning letters related to promotional issues. In the two years since *Caronia*, the FDA has issued only three. Untitled letters for promotional issues similarly fell from sixty-three to thirty-one in the same period.[32] It may be that companies' enhanced and maturing compliance programs--after more than a decade of heavy enforcement--are bearing fruit, reducing the number of situations in which the government can take action, at least without running afoul of First Amendment protections.

The most notable warning and untitled letters in 2014 were:

- **Warning Letter of September 23, 2014:** The FDA issued its only warning letter of 2014 to a specialty pharmaceutical company, raising concerns about its marketing of a local anesthetic designed for postsurgical use via educational flashcard administration guides and a journal advertisement.[33] Noting that the educational guides covered procedures for which the drug had not yet been demonstrated to be safe and effective, the FDA found that the guides were evidence of intended off-label use. The FDA also determined the journal advertisement was misleading because it overstated the duration of pain control provided by the drug. The FDA directed the company to issue "complete corrective messages" through the same media used to disseminate the problematic promotional materials.

- **Untitled Letter of February 24, 2014 Regarding Facebook Page:** In February, the FDA took issue with a Facebook page that a pharmaceutical company created for its hypothyroidism treatment drug.[34] The FDA found the Facebook page had made suggestions regarding the use of the drug for patients with hypothyroidism, but failed to disclose limitations on the drug's approved hypothyroidism-related uses. The FDA also found the page to be misleading because it made representations about the efficacy of the drug but failed to communicate any information regarding risks. This enforcement action was the first following the FDA's January 2014 draft guidance regarding the promotion of drugs through interactive promotional media, discussed below.

B. DOJ Enforcement Activity – Advertising and Promotion

The DOJ continued to secure a steady stream of large off-label promotion settlements in 2014 in the wake of the record-setting recoveries in recent years, including a $2.2 billion global settlement of off-label promotion allegations within the 2014 fiscal year, announced in late 2013.[35] Among the notable promotional settlements of 2014 were:

- On January 9, 2014, a pharmaceutical and medical technology company agreed to pay $40.1 million to resolve *qui tam* allegations involving alleged kickbacks and off-label promotion relating to a pre-surgical skin preparation product.[36] The settlement resolves allegations that, during the period between September 2009 and August 2011, the company knowingly promoted the sale of its product for uses not approved by the FDA.

- On April 16, 2014, a pharmaceutical company agreed to pay $7.5 million to resolve allegations stemming from a *qui tam* suit by a former sales representative that the company violated the FCA in connection with its off-label marketing of a pediatric drug.[37] The settlement resolves allegations that between 2005 and 2010, the company knowingly promoted the drug for a use not approved by the FDA.

- On February 21, 2014, a global specialty health care and pharmaceutical company agreed to pay $192.7 million to resolve criminal and civil liability for alleged violations of the FCA and the FDCA.[38] The company also entered into a CIA with HHS OIG that will govern the company's ongoing practices. The settlement resolved allegations that between 1999 and 2007, the company promoted and sold a prescription drug for unapproved uses, in violation of the FDCA's misbranding provisions, and caused the submission of false claims for payment to the government relating to the same product.

- On September 24, 2014, a pharmaceutical company agreed to pay $56.5 million to resolve allegations that it violated the FCA as a result of its marketing of several drugs. The settlement resolves allegations made in two *qui tam* suits of alleged misconduct that occurred from January 2004 and December 2007, including off-label promotion and false and misleading statements about the efficacy of the drugs.[39]

In addition to the thriving enforcement activity at the federal level, 2014 saw the states continue their aggressive enforcement of advertising, unfair trade practices, and consumer protection laws in response to allegedly misleading or off-label promotion.[40] Among the notable state settlements of 2014 were:

- On June 4, 2014, a multinational pharmaceutical and health care company agreed to pay $105 million to 44 states and the District of Columbia to resolve allegations that the company improperly promoted several drugs for off-label uses and concealed risks relating to another drug.[41] As part of the settlement, the company also agreed to a five-year CIA with HHS OIG that includes several strict compliance provisions, including placing limitations on its ability to promote its products, respond to off-label inquiries, and provide educational grants and funding.[42]

- On August 6, 2014, a multinational pharmaceutical corporation agreed to pay $35 million to 41 states and the District of Columbia to resolve alleged improper marketing practices and off-label promotion.[43] The company allegedly promoted an immunosuppressive drug for uses that were not FDA-approved and violated state consumer protection laws by misrepresenting the uses and benefits of that drug through the funding of promotional speaking engagements and studies.

C. FDA's Regulatory Policy and Draft Guidance

Although many had hoped that the FDA would overhaul its policies to better reflect the courts' recognition of First Amendment protections for promotional speech, no drastic changes materialized in 2014. In the meantime, technological advances and a shift in advertising toward electronic and social

media also have raised real questions about how the FDA enforcement of the FDCA's misbranding rules will operate in the future.

In April 2014, the FDA's Chief Counsel stated that "the agency is taking . . . first amendment concerns very seriously" and that the FDA is "carefully evaluating" its drug advertising and promotional policies "in light of court decisions on first amendment issues," with the goal of "realign[ing] FDA regulatory posture in this area."[44] Then, on June 6, 2014, the FDA issued a long-awaited response to a pair of citizen petitions from 2011 and 2013 filed by a coalition of biopharmaceutical and medical technology developers. In the wake of significant First Amendment judicial decisions, the citizen petitions had requested that the agency clarify its regulations and policies on manufacturer dissemination of scientific and medical information relating to off-label uses.[45] The FDA agreed to provide "greater regulatory clarity" by year-end and more generally engage in a "comprehensive review of the regulatory regime governing communications about medical products."[46]

The FDA did not announce wholesale changes in its approach to such communications, but it did update or issue draft guidance in several related areas during 2014, including: draft guidance on promotional activity on the internet and social media; updated draft guidance on distributing scientific and medical publications regarding off-label uses; and draft guidance on distributing scientific and medical publications regarding risk information for approved product uses.

1. Using Social Media to Promote FDA-Approved Products

The FDA released three sets of highly anticipated draft guidance in 2014 related to the use of Internet and social media platforms to promote and communicate about FDA-approved products. As nearly half of pharmaceutical manufacturers are reported to be actively using social media to promote their products, the FDA's guidance was a much-needed first step in the process, even if the guidance has not been well received in its present form.[47]

a) Draft Guidance on Internet/Social Media Platforms with Character Space Limitations--Presenting Risk and Benefit Information for Prescription Drugs and Medical Devices

In June 2014, the FDA issued draft guidance relating to the promotion of drugs and medical devices on the Internet and social media platforms with character space limitations, such as Twitter, as well as sponsored site link advertisements.[48] The guidance primarily counsels pharmaceutical manufacturers to ensure that their communications on these platforms provide "balanced" risk and benefit information. Recognizing the challenges that character limits pose, the FDA approved the use of truncated risk statements, so long as the communication discloses the most serious risks and provides a direct hyperlink to a more complete discussion of the product's risk, dosage, and quantitative ingredient information. As a result of this draft guidance, the use of Twitter and other limited-character platforms for drug and device promotion may be limited to simple "reminder" messaging with product names, rather than the next significant tool for touting a product's benefits.

Key industry groups criticized the draft guidance as contrary to the First Amendment and also raised questions regarding whether the FDA understands the technology underlying sponsored links from

web giants such as Google.[49] Device manufacturers also commented that the guidance exceeds the FDA's regulatory authority and fails to address clearly the distinction between drugs and devices, and requested separate promotional guidance for FDA-regulated devices.[50]

b) Draft Guidance on Internet/Social Media Platforms: Correcting Independent Third-Party Misinformation About Prescription Drugs and Medical Devices

In June, the FDA also released draft guidance regarding how drug and device manufacturers may respond to product misinformation posted by third parties on social media or other Internet platforms.[51] The FDA's draft guidance requires any communications by the company to be consistent with the FDA-approved product labeling, non-promotional, and limited to the scope of the misinformation. The FDA also counsels companies to keep records regarding corrective communications so that they can respond to FDA inquiries as necessary. Although the FDA's draft guidance is an important first step, it leaves some open questions. For example, if a company decides to correct third-party misinformation, it is unclear whether the FDA expects the company to update or respond to ongoing real-time discussion on the same platform.

c) Draft Guidance on Postmarketing Submissions of Interactive Promotional Media for Prescription Human and Animal Drugs and Biologics

In January, the FDA issued draft guidance on the application of postmarketing reporting requirements under the FDCA to the promotion of drugs through interactive media, (i.e., web-based platforms that "allow for real-time communications and interactions," including "blogs, microblogs, social networking sites, online communities, and live podcasts").[52] The FDA's draft guidance directs companies to submit to the FDA the content of all websites they own, control, create, "influence," or operate. Under the draft guidance, the FDA will not consider user-generated content on sites for which the firm is responsible "as promotional content on behalf of the firm as long as the user has no affiliation with the firm and the firm has no influence on" the user content. Although the FDCA requires the submission of promotional pieces "at the time of initial dissemination," the FDA "intends to exercise enforcement discretion" to address real-time communications through interactive media. The draft guidance leaves some important questions unanswered, such as how broadly the FDA will construe the term "influence" and how the restrictions will comport with First Amendment protections.

2. Distributing Scientific and Medical Publications on Unapproved Uses

In February, the FDA issued a draft revision of its 2009 guidance on the manner in which drug and device manufacturers may distribute scientific and medical publications on unapproved new uses of drugs and devices.[53] The FDA's new draft guidance provides that such publications should be developed or reviewed by experts, adequately disclose conflicts of interest, avoid promoting any unapproved uses, and not be edited or influenced by the manufacturer. The draft guidance adds some clarity to the FDA's expectations, but the principles underlying the draft guidance appear to remain fundamentally unchanged from 2009. Further, the draft guidance does not appear to reflect recent First Amendment jurisprudence. If the FDA elects to pursue enforcement actions based on distribution of

materials in a manner that does not conform to the draft guidance but is nonetheless truthful and not misleading, it may well generate new First Amendment challenges.

3. Distributing Scientific and Medical Publications on Risk Information for Approved Prescription Drugs and Biological Products

Recognizing that new risk information often comes to light as a result of postmarketing pharmacovigilance activities, the FDA issued draft guidance in June 2014 allowing drug manufacturers to present newly discovered risk information to health care providers.[54] Importantly, this draft guidance applies only to new risk information that "rebuts or mitigates information" about an already identified risk; it does not apply to information about newly identified risks or to information indicating that an existing risk is more serious than reflected in the approved labeling. Under the draft guidance, the information distributed should be based on a study or analysis published in an independent, peer-reviewed journal, and should be "at least as persuasive as the data sources that underlie the existing risk assessment . . . as reflected in approved labeling." The conclusions of the study should account for and fairly characterize "all relevant information in the safety database, including contrary or otherwise inconsistent findings."

D. Notable Case Law Developments

In 2014, courts continued to grapple with the FDCA's boundaries regarding off-label drug and device promotion. Although some courts adhered to the view that off-label promotion violates the FDCA, others have indicated the importance of drawing a distinction between truthful off-label promotion and false or misleading off-label promotion. The First Circuit and district courts in the First and Third Circuits also issued rulings that may limit potential civil FCA liability in cases involving allegations of off-label promotion.

1. Courts Continue to Differ on the Boundaries of Off-Label Promotion under Federal Law

No new circuit-level decisions emerged in 2014 directly addressing the contours of unlawful off-label promotion. But many courts continued to make broad pronouncements that the FDCA prohibits companies from marketing products for "off-label" uses. In the absence of clearer guidance from the circuit courts, district courts across the country have reached differing conclusions on the issue. Other district courts have avoided resolving whether off-label promotion violates the FDCA by concluding that, at a minimum, the statute "prohibits false or misleading off-label promotion" of FDA-approved drug and devices.[55] For the time being, although the risk of enforcement for any off-label promotion remains high, companies are more likely to face misbranding charges and related liability if the off-label promotion at issue is false or misleading.

One of the year's most interesting developments came in a declined *qui tam* case shaping up as a battle over the government's regulatory authority in this area. That case, *United States ex rel. Solis v. Millennium Pharmaceuticals*, involves allegations that the defendant promoted off-label use through the dissemination of published medical literature.[56] The Pharmaceutical Research and Manufacturers of America ("PhRMA") intervened and filed an *amicus* brief in support of the

defendant's motion to dismiss, arguing that the conduct in question was protected by the First Amendment and therefore could not be the basis for liability under the FCA.[57] After unsuccessfully opposing PhRMA's intervention, the government filed a vehement statement of interest in opposition, characterizing PhRMA's position as "radical" and "extreme" and arguing that the use of off-label marketing as evidence of intent does not run afoul of the First Amendment.[58] The government's statement asserted that such conduct can be used as evidence of intent in FCA cases.[59] The district court is set to hear the defendants' motion to dismiss in *Solis* in late January 2015.

2. Courts Continue to Hold that the FDCA Preempts State Law Claims Based on Truthful Off-Label Promotion

The year also saw courts continue to hold that the FDCA impliedly preempts state law claims based on off-label promotion, absent any parallel state law duty to refrain from such promotion. The distinction between truthful and misleading speech similarly played an important role in setting the boundaries of the FDCA's preemptive effect.

In June, the Sixth Circuit issued an important decision in *In re Darvocet, Darvon, & Propoxyphene Products Liability Litigation*, dismissing state law negligence claims based on alleged drug misbranding.[60] The court held that the FDCA preempted the state law claims "[s]ince the conduct that Plaintiffs allege gives rise to their statutory negligence claims is the [defendants'] violation of the FDCA"--a statute that the federal government alone has the power to enforce.[61] The decision also is one of the first to discuss a so-called "parallel misbranding" theory of liability under state law. The plaintiffs argued that their state law claims paralleled the FDCA's misbranding provisions and thus were not preempted. The Sixth Circuit expressed skepticism over the viability of plaintiffs' attempt to advance this "parallel misbranding" theory, but ultimately held that even if such claims are not preempted, the plaintiffs had failed to plead one.[62]

Primarily in the medical device context, a number of district courts similarly ruled that the FDCA preempts state law claims predicated on allegations of off-label promotion. Central to the reasoning in each of these decisions is the fact that there is "no state-law duty to refrain from off-label promotion."[63] The courts generally drew a distinction, however, between truthful off-label promotion and off-label promotion with a false or misleading element. Whereas state laws may not prohibit off-label promotion *per se*, many state laws do impose an independent duty to refrain from false and misleading conduct. Thus, where state law claims are based on off-label promotion that was also false or misleading, courts have found a basis for liability independent of the FDCA and have declined to give the FDCA preemptive effect.

3. Courts Limit Potential Avenues of Liability in Civil FCA Cases Involving Off-Label Promotion

In April, the First Circuit issued a decision relating to the FCA's first-to-file bar, with important implications for off-label marketing cases. In *United States ex rel. Wilson v. Bristol-Myers Squibb, Inc.*, the court held that the first-to-file bar can apply even where an earlier filed case is based on alleged off-label promotion of the same drug for different unapproved uses.[64] In *Wilson*, the

dismissed case and the prior action both involved allegations that the defendants had engaged in "broad, nationwide schemes to promote and prescribe" certain drugs for "off-label uses."[65] Even though the alleged off-label uses related to "different diseases and symptoms" in the two cases, the court determined that "those differences are not enough" to preclude application of the first-to-file bar.[66] Given the frequency with which off-label drug cases involve alleged nationwide schemes, the First Circuit's decision may prove useful where companies face successive lawsuits and the underlying details of the alleged off-label promotion scheme differ in each case.

In March and April, two district courts dismissed FCA *qui tam* claims after concluding that the relators had not alleged that compliance with the FDCA's misbranding provision was a condition of payment by the government. In March, in *United States ex rel. Booker v. Pfizer, Inc.*, the District of Massachusetts rejected the argument that drugs allegedly misbranded under the FDCA due to off-label promotion rendered related claims for payment false, finding that "[n]othing in [the plaintiff's] complaint even remotely alleges that any of the federal or state programs at issue make compliance with marketing regulations or criminal misbranding laws a precondition to payment."[67] Similarly, in *United States ex rel. Simpson v. Bayer Corp.*, the District of New Jersey dismissed FDCA claims predicated on allegations that a manufacturer's promotion of a drug rendered that drug misbranded under the FDCA.[68] The court found that the relator had not sufficiently alleged that "compliance with the FDCA's misbranding provisions was a condition of payment" by any of the government programs allegedly defrauded.[69]

III. Developments in cGMP Regulations and Other Manufacturing Issues

Under the FDCA, the FDA has promulgated cGMP regulations for drug products and the quality system regulation ("QSR") for medical devices. Compliance with these rules is a highly technical, but critical, effort; failure to adhere to cGMPs may provide the basis for enforcement action--civil, criminal, or both--even if the products at issue actually pose no safety risk. Government agencies have generally reserved the most serious enforcement activity for situations in which the FDA perceives a significant risk to public health and safety.

As noted above, manufacturing issues have become particularly prominent in recent years due to a number of high-profile public health issues stemming from deficient manufacturing processes. Below, we address key developments in cGMP regulatory compliance in 2014, in the following areas: cGMP compliance and enforcement trends; recent case law developments; an agency reorganization that could impact the government's cGMP enforcement efforts; and the FDA's 2014 rulemaking and guidance activity bearing on manufacturing issues.

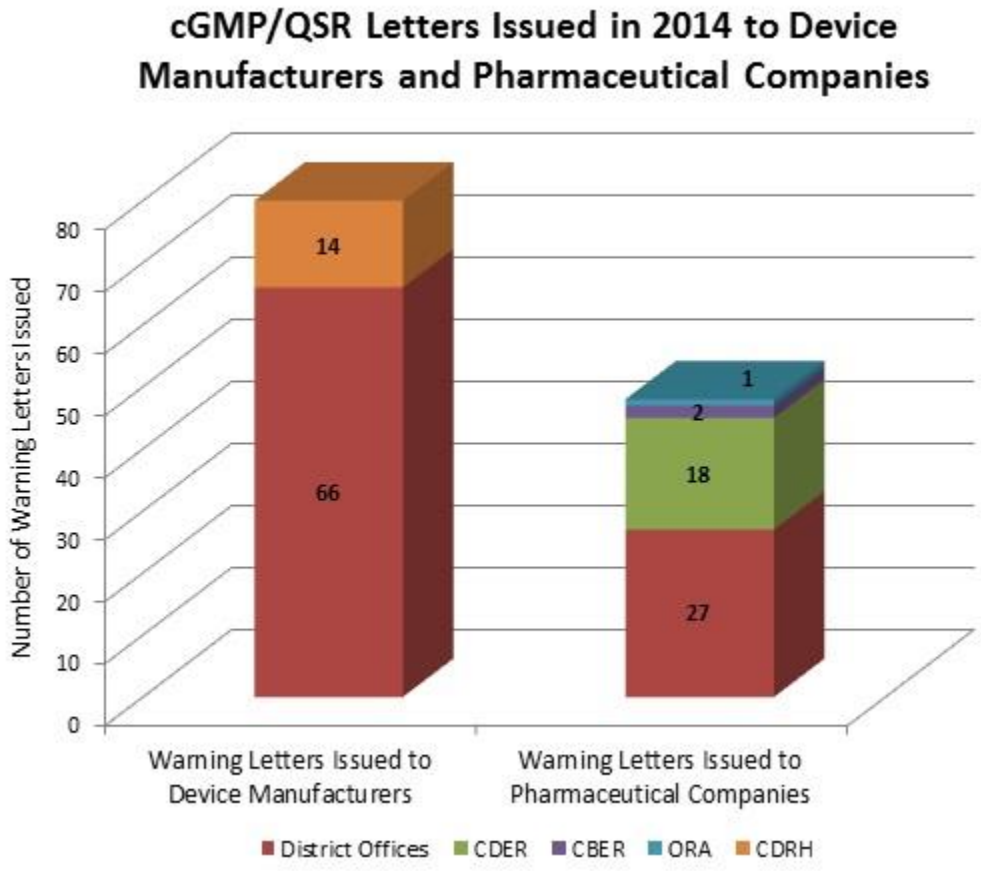
A. 2014 cGMP Compliance and Enforcement Trends

Early in 2013, a DOJ official stated that ensuring compliance with good manufacturing practices would be one of the Department's "top area[s] of focus."[70] Indeed, 2013 saw the DOJ conclude its "largest drug safety settlement to date with a generic drug manufacturer" when a U.S. subsidiary of Ranbaxy Laboratories Limited ("Ranbaxy") agreed to pay a criminal fine and forfeiture totaling $150 million and settled civil claims under the FCA and related state laws for $350 million in connection

with manufacturing issues in two of its facilities in India.[71] Ranbaxy also pled guilty to felony charges for violating the FDCA and knowingly making material false statements to the FDA. This past year, Assistant Attorney General Stuart F. Delery focused on the DOJ's settlement with Ranbaxy and announced a "renewed emphasis on identifying non-monetary measures that will help . . . prevent the recurrence of misconduct."[72]

In recent years, the FDA also has emphasized the global reach of FDA requirements for cGMP compliance. In the wake of highly publicized issues at facilities operated by Ranbaxy, Wockhardt, Sun Pharmaceutical, and others,[73] FDA Commissioner Margaret Hamburg made her first official trip to India and stated that the FDA intended to expand its presence in that country.[74] China also continues to be a major focus for the agency. On November 17, 2014, Commissioner Hamburg remarked in a speech at Peking University that as China's medical products industry has matured, it has encountered compliance and quality control problems, citing the development of numerous small companies that lack the appropriate systems to ensure cGMP compliance.[75] Earlier in the year, FDA's Country Director for China stated that the FDA sought funding to broaden its range of inspectional capabilities.[76] Consistent with these statements from FDA officials, the FDA's Fiscal Year 2015 budget request projected increases in the number of cGMP/QSR inspections for both foreign drug and device manufacturers.[77]

While the DOJ announced a number of settlements with and verdicts against food and dietary supplement manufacturers related to cGMP issues in 2014,[78] there were relatively few high-profile prosecutions or monetary settlements involving drug and device manufacturers. There is little doubt, however, that cGMPs will continue to be a significant focus of FDA enforcement efforts.[79] For the 2014 calendar year, at least forty-eight FDA warning letters to companies involved in the manufacture and/or compounding of drugs cited violations of drug cGMP regulations. District offices issued the majority of the letters categorized as cGMP-related (twenty-seven), while the remaining letters came from the Center for Drug Evaluation and Research ("CDER"), the Center for Biologics Evaluation and Research ("CBER"), and the Office of Regulatory Affairs ("ORA"). Medical device manufacturers were more frequently targeted for cGMP enforcement; the FDA issued at least eighty warning letters categorized as involving cGMP/QSR violations to those companies (fourteen from the Center for Devices and Radiological Health ("CDRH") and sixty-six from district offices).



Source: U.S. Food & Drug Admin.[80]

According to the agency's Inspectional Observations Summaries data, the FDA's emphasis on cGMP compliance may be working: the number of Form 483s issued during Fiscal Year 2014 decreased from Fiscal Year 2013, as part of an overall downward trend in Form 483s since Fiscal Year 2011.[81] The top five most commonly cited Form 483 observations for the drug and device product categories in Fiscal Year 2014 are summarized below and show little variation from recent years. In fact, the top Form 483 observation for the device category has remained unchanged for the past five years, and the top drug observation has been constant since Fiscal Year 2006, the first year for which information from the FDA's TURBO EIR System is readily available.[82]

Top Drug 483 Observations FY 2014		Top Device 483 Observations FY 2014	
Number of Observations	**Short Description**	**Number of Observations**	**Short Description**
145	Procedures not in writing, not fully followed	360	Lack of or inadequate procedures
109	Scientifically sound laboratory controls	251	Lack of or inadequate complaint procedures
94	Investigations of discrepancies, failures	129	Purchasing controls, Lack of or inadequate procedures
87	Absence of Written Procedures	122	Lack of or inadequate process validation
72	Written procedures not established/followed *tied with* Procedures for sterile drug products	117	Lack of Written MDR Procedures

B. The Fourth Circuit Limits the Scope of False Claims Act Liability for cGMP Violations in *United States ex rel. Rostholder v. Omnicare, Inc.*

In February, the Fourth Circuit handed down an important opinion in *United States ex rel. Rostholder v. Omnicare, Inc.*, regarding the viability of cGMP violations as a predicate for FCA liability.[83] There, the relator alleged that his employer pharmacy handled penicillin, which presented contamination concerns related to an affiliated repacking company's non-penicillin products. After he resigned, the relator provided information to FDA officials, which resulted in FDA inspections of the company's manufacturing facility and, ultimately, the issuance of a warning letter to the facility that outlined various cGMP violations, including with respect to the handling of penicillin. The relator then filed suit under the FCA alleging that the drugs repackaged at the facility were "adulterated" under the FDCA and that the defendant therefore committed "fraud" by selling those drugs and then receiving reimbursement from government programs.

The Fourth Circuit rejected the relator's contentions, holding that the alleged misconduct was not actionable under the FCA because compliance with cGMPs and other FDA safety regulations is not an explicit '"prerequisite to gaining a [government] benefit."'[84] Further, the court noted that "[t]o qualify as a 'covered outpatient drug' as defined in the Medicare and Medicaid statutes [and as necessary to be reimbursable], a drug merely must be *approved* by the FDA," and the drug at issue was approved.[85] The Fourth Circuit recognized that accepting the "relator's theory of liability based merely on a regulatory violation . . . would sanction use of the FCA as a sweeping mechanism to

promote regulatory compliance, rather than a set of statutes aimed at protecting the financial resources of the government from the consequences of fraudulent conduct."[86] Indeed, "[w]hen an agency has broad powers to enforce its own regulations, as the FDA does . . . , allowing FCA liability based on regulatory non-compliance could short-circuit the very remedial process the Government has established to address non-compliance . . . ."[87]

In October, the Supreme Court denied the relator's petition for review.[88] Thus, *Rostholder* continues to stand for the proposition that a cGMP violation--indeed, any regulatory violation--cannot provide the basis for an FCA action on its own; rather, a violation of a regulation or law is only actionable under the FCA if payment is expressly conditioned on compliance with that regulation or law. This concept, which other circuits have recognized over the years as well, is critical for defendants responding to so-called "false certification" claims.

But the viability of cGMP-related theories of liability under the FCA is unlikely to be a closed issue, because the *Rostholder* court was not presented with allegations that the drugs allegedly bought by the government were *actually* adulterated or altered in some way that would mean that the government health program was not getting the drug it thought it was paying for. Indeed, the government's statement of interest in *Rostholder* argued that "the deficiencies in the drug resulting from the cGMP violations may impact the government's decision to pay a claim for the drug," and thus "the violation of cGMP regulations may be relevant in FCA cases where the violations are significant, substantial, and give rise to actual discrepancies in the composition or functioning of the product."[89] Although the DOJ and the FDA did not use *Rostholder* as a vehicle to advance such a position, it is possible that the government will do so in future FCA cases with more favorable facts.[90]

C. FDA Reorganization

Recent years have seen new statutory mandates add to and alter the FDA's responsibilities. As a result, the agency has apparently been rethinking its office structure and personnel deployment. In 2014, the agency announced major reorganizations that will shuffle the administrative oversight structure for cGMP compliance, including oversight of inspections and enforcement activities. As more specifics emerge during 2015, we expect that the practical effect of the FDA's internal changes for FDA-regulated industry will become more apparent.

1. FDA Commissioner and Regulatory Programs Respond to Program Alignment Group Recommendations

FDA inspections are the front line of the agency's cGMP oversight activity and one of the most important interactions that drug and medical device manufactures have with the FDA. Currently, inspections and enforcement operations are organized regionally by FDA district offices. Certain districts may assign investigators on the basis of product expertise, while others require investigators to cover a broader range of products. As a result, the nature of an FDA inspection for a manufacturer may vary depending on the geographic location of its facilities. However, recommendations from the FDA's internal Program Alignment Group indicate that the current organization is likely to change.[91]

In a February 3, 2014 memorandum, Commissioner Hamburg described, among other changes, the FDA's plans to reorganize its compliance and regulatory functions into "commodity-based . . . and vertically-integrated regulatory programs" that will include specialized inspection forces in commodity-specific offices. The categories for those regulatory programs break down as follows:

1. Pharmaceutical quality (includes drugs and biologics regulated by CDER and veterinary drugs);
2. Food and feeds;
3. Medical devices and radiological health;
4. Products regulated by CBER;
5. Tobacco; and
6. Bioresearch Monitoring.

The ORA, which currently manages both foreign and domestic inspection and compliance activities for FDA-regulated products, will centrally manage the specialized inspection forces when the reorganization is implemented.[92] But the February 3, 2014 memorandum also identified "layers" of authority within the FDA as barriers to clearer and more efficient compliance and enforcement policies. Thus, Commissioner Hamburg adopted the Program Alignment Group's recommendation that the Centers have primary responsibility to develop compliance policies and enforcement strategies in consultation with the ORA. She also directed the Centers to de-layer internal review levels where possible.

The training and specialization envisioned for the reorganization presumably will lead to a more uniform inspection experience for FDA-regulated enterprises. According to the Commissioner, the goal is to ensure that the FDA "speaks with one voice on policies and operations related to any given commodity."[93] Moreover, as the Medical Device Action Plan in response to the recommendations observes, this central control also will allow the FDA to develop specific areas of expertise among investigators.[94]

2. CDER Shifts Functions to New Office of Pharmaceutical Quality

In addition to the internal reorganization prompted by the Program Alignment Group's Recommendations, CDER's previously proposed shift of many quality-related functions to the new Office of Pharmaceutical Quality ("OPQ") will finally occur in January 2015.[95] CDER Director Janet Woodcock will be "acting" head of OPQ, the new "super office" intended to unify all non-enforcement pharmaceutical quality oversight for new, generic, and over-the-counter drug products regardless of whether such products are manufactured at foreign or domestic sites. As a result, certain inspection responsibilities will shift among offices: the Office of Compliance will turn over preapproval and surveillance inspection activities to OPQ, and bioequivalence/bioavailability and non-clinical study inspection activities will move from the Office of Compliance to the Office of Translational Sciences. In theory, these shifts should leave the Office of Compliance with more time to focus on enforcement efforts.

D. cGMP Rulemaking and Guidance Activity

1. Compounded Drugs

Motivated in part by the meningitis outbreak traced to contaminated steroid injections compounded at the New England Compounding Center, Congress passed the Drug Quality and Security Act ("DQSA"), which includes oversight provisions related to compounding human drugs in 2013.[96] The DQSA amends FDCA Section 503A to set forth circumstances in which some compounded drugs may be exempt from certain FDA requirements; namely, cGMP compliance, labeling with adequate directions for use, and premarket FDA approval.[97] To qualify for a Section 503A exemption, a facility may not compound drugs absent a prescription for an individually identified patient. In addition, under new FDCA Section 503B, compounders may voluntarily register with the FDA as "outsourcing facilities."[98] Although outsourcing facilities may qualify for the other two exemptions provided to compounders, they will not be exempt from cGMP requirements and will be subject to FDA inspection according to a risk-based schedule. Publicly available FDA records reveal that there are currently twenty-eight voluntarily registered outsourcing facilities.[99]

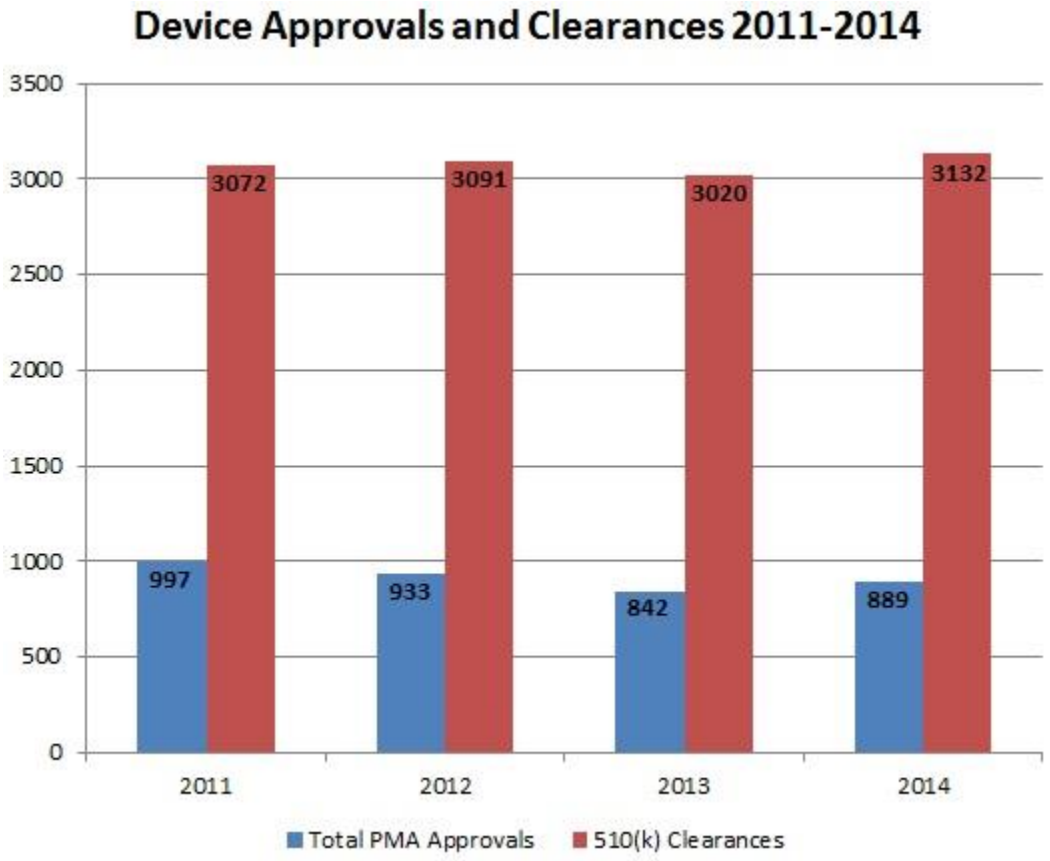
The FDA took several initial steps to implement the DQSA in 2014, including issuing draft and final guidance documents such as its interim guidance on cGMPs for registered outsourcing facilities.[100] The draft guidance describes the FDA's current expectations for outsourcing facility compliance with the drug cGMPs codified at 21 C.F.R. Parts 210 and 211 until the agency promulgates cGMP regulations specific to outsourcing facilities.[101] The draft guidance distinguishes the application of cGMPs to outsourcing facilities from the typical application in a number of areas, such as sterility and depyrogenation testing, identity testing, and release testing.[102]

The FDA specifically requested public comment on possible approaches to reduce the need for outsourcing facilities to conduct laboratory testing and proposed two alternatives.[103] The first alternative approach relates to testing of incoming drug components after initial qualification testing. Under this alternative, an outsourcing facility could forego follow-up testing on components if the component supplier submits a drug master file ("DMF") meeting certain criteria outlined in the draft guidance to the agency.[104] The outsourcing facility would also need to maintain a copy of a letter from the FDA to the DMF holder stating that the agency has no further questions after review of the DMF to produce during inspections. The FDA similarly proposed to have third-party laboratories submit DMFs upon which outsourcing facilities could rely (if all other criteria in the draft guidance are met) as a way to minimize outsourcing facilities' need to have in-house laboratories perform final release testing.[105]

The extent to which the FDA applies existing drug cGMP requirements to outsourcing facilities in the final guidance (and, eventually, the development and implementation of outsourcing-specific cGMP regulations) may ultimately be a major factor in the success of the DQSA's voluntary registration program. However these new rules play out, compounders likely will continue to be a central focus of enforcement activity in the ensuing years as the agency uses its new authority under the DQSA.

IV. Medical Devices

In February 2014, CDRH unveiled its strategic priorities for 2014 and 2015. In that document, CDRH pledged to focus on: "strengthen[ing] the clinical trial enterprise" in the United States by enhancing the efficiency and predictability of the investigational device exemption ("IDE") process; "strik[ing] the right balance" between ensuring the safety and effectiveness of medical devices and allowing patient access to devices (i.e., the balance between premarket and postmarket data collection); and "provid[ing] excellent customer service" to industry stakeholders.[106] Meanwhile, in the 2014 calendar year the FDA approved 889 Premarket Approval ("PMA") applications--including twenty-five original PMA approvals--and 3,132 510(k) clearances, approximately in line with recent years.



Source: U.S. Food & Drug Admin., Ctr. for Devices & Radiological Health[107]

Although CDRH's success this past year in meeting its strategic goals remains to be seen, it is clear that 2014 saw a number of significant developments for medical device manufacturers and other entities that may--if the FDA has its druthers--become subject to medical device regulations. Below, we address the FDA's release of historical Quality System Data; assorted new FDA guidance for medical device manufacturers; and significant case law developments regarding the scope of the FDA's authority over device makers.

A. FDA Release of Quality System Data

In May 2014, CDRH released three years' worth of data (2010 to 2012) related to its inspections of medical device manufacturing plants.[108] By releasing this data as part of its Transparency Initiative and Case for Quality, the FDA sought to "support[] better quality medical devices and communications with industry."[109] CDRH followed up with a summary of 2013 inspections in September, which outlines the FDA's recent history in issuing Form 483 inspectional observations and warning letters.[110]

So what lessons can medical device manufacturers take from this data dump? First, the FDA has increased the number of inspections it conducts every year, and appears to have zeroed in on manufacturers operating abroad--but the FDA's capacity for conducting inspections of device manufacturers may be reaching a peak. In 2012, the FDA reported that the number of total quality system surveillance inspections "increased by 37 percent overall and for foreign firms it has increased by 93 percent."[111] This number effectively decreased by 3% in 2013, a drop that the FDA attributed to a higher rate of foreign inspections, which require more agency resources to complete.[112] Second, manufacturers in China are increasingly likely to host FDA inspectors--the FDA conducted eighty-two inspections in China in 2013, and the data indicates that most of those inspections were considered Level 2, "comprehensive" inspections.[113] And FDA noted that foreign firms are four times as likely to receive warning letters as a result of inspections as domestic firms.[114] Third, the most common violations cited in warning letters have not changed much over time--issues with corrective and preventive action procedures, complaint handling, and quality audit procedures still lead the way.[115]

B. New FDA Guidance

The past year saw FDA issue several guidance documents in a wide variety of areas impacting medical device manufacturers.

1. 510(k) Program

In July, FDA released new, long-awaited guidance on the 510(k) clearance process, providing manufacturers with insight into the process by which the agency determines whether a medical device is substantially equivalent to an existing device on the market.[116] This is important, of course, because a determination that the device is substantially equivalent allows manufacturers to forego the PMA process. The FDA issued this revised guidance with an eye toward "enhanc[ing] the predictability, consistency, and transparency of the 510(k) program by describing in greater detail the regulatory framework, policies, and practices underlying FDA's review of 510(k) premarket notifications."[117]

Manufacturers should take note of a few developments arising out of this new guidance. First, there is a new "510(k) Decision-Making Flowchart," which supersedes a similar flowchart originally issued in 1986.[118] Second, FDA will no longer allow manufacturers to rely on "split predicates" to establish that a new device is substantially equivalent in intended use to an existing product, but substantially equivalent in its technological characteristics with a different existing product.[119] Manufacturers

may still use additional predicates to support claims of substantial equivalence, but the FDA asserted that manufacturers will be required to support their claims under each step of the 510(k) process using a single predicate device.[120] The new guidance gives examples of types of multi-predicate equivalence that may suffice, such as a hemodialysis catheter having two predicates with the same intended use as the new device; two bone fixation plates having different indications for different areas of a bone, but the same intended use; and predicate devices for laser technology having the same intended use *and* the same technological characteristics as the new device.[121]

That said, the FDA will continue revising existing 510(k) guidance; the agency noted in the July guidance that it intends to finalize new sections on "Special" and "Abbreviated" 510(k) programs in the future.[122] In October, the FDA finalized guidance regarding the information relating to cybersecurity that must be included in 510(k) clearance applications (as well as in PMA applications and *de novo* submissions).[123] And in December, the agency released new draft guidance clarifying the process by which manufacturers should notify the FDA of transfers of 510(k) clearance to other companies, as well as the process by which the FDA will make public and transparent the current holders of 510(k) clearances.[124]

2. *De Novo* Classification Process for Devices

This past year, the FDA also released new draft guidance on the *de novo* approval process for devices that do not have a predicate device but are low to moderate risk (thereby rendering the PMA process unduly burdensome).[125] Absent the *de novo* process, devices that have not been previously classified by the FDA historically received an automatic "Class III" classification. Before the passing of the Food and Drug Administration Safety and Innovation Act ("FDASIA") in 2012, a device could not proceed through the *de novo* process unless it had been subject to the 510(k) clearance process and deemed not substantially equivalent to existing devices. The FDASIA, however, provides that a device manufacturer may submit a *de novo* petition without first going through the 510(k) process.[126] The FDA's guidance details how to file such a petition and what to include in it. But FDA also recommended that *de novo* applicants should request a pre-submission meeting before submitting the petition.[127]

3. Custom Devices

In September, the FDA issued final guidance regarding the custom device exemption to the standard approval or clearance process.[128] The guidance implements requirements included in the FDASIA. According to the guidance, "custom devices should represent a narrow category for which, due to the rarity of a patient's medical condition or physician's special need, compliance with premarket review requirements and performance standards . . . is impractical."[129] Among other requirements that narrow the scope of this category, custom devices must not be generally commercially available in finished form for distribution in the United States, must be manufactured on a case-by-case basis, must be intended to treat a unique disease or condition that other available devices cannot treat (and that disease or condition must be so rare that a clinical study of the device would be impractical).[130] The device need not be entirely unique--but only five units of the device annually may be covered by the exemption.[131]

4. Laboratory Developed Tests

In 2014, the FDA also took steps toward active regulation of Laboratory Developed Tests ("LDTs") as medical devices--and sparked controversy in the process. LDTs are diagnostic tests designed, manufactured and performed in clinical laboratories (e.g., for genetic conditions). In the past, research laboratories often developed these types of tests to identify uncommon diseases; as a result, the tests were performed rarely and generally were overseen and interpreted by scientific experts.[132] But recent testing advances--including those diagnosing certain types of cancer--and a focus on personalized medicine indicate that LDTs likely will continue to proliferate.[133]

According to the FDA, the agency historically has not actively regulated LDTs as devices because, at the time of the Medical Device Amendments to the FDCA, such tests were developed and performed in small volumes. However, the FDA has maintained that LDTs are *in vitro* diagnostics ("IVDs") encompassed by the definition of "device" under the Amendments.[134]

On October 3, 2014, FDA released two draft guidance documents designed to give industry insight into how the agency intends to regulate LDTs, on the basis that they are now more sophisticated and made outside health care providers' laboratories. According to the FDA, absent "appropriate oversight of LDTs, there is the potential for increased risk to patients."[135]

In one of the draft guidance documents, the FDA described the general regulatory framework it envisions for LDTs.[136] There, the FDA set forth what it sees as a "risk-based framework" for enforcing the FDCA and regulations thereunder against laboratories that manufacture LDTs.[137] According to the FDA, LDTs are IVDs "intended for clinical use and designed, manufactured and used within a single laboratory."[138] Generally speaking, the guidance proposes to classify LDTs like other devices (Class I, Class II, or Class III), and the FDA intends to require laboratories to abide by registration, listing, and manufacturer reporting requirements immediately after the guidance takes effect.[139] The FDA plans to phase in premarket review and quality system regulation requirements on a risk-based timeline thereafter.[140] The agency also intends to release further guidance regarding whether and under what circumstances LDTs will be categorized as Class I, Class II, or Class III devices.[141] But the FDA indicated that it does not intend, for the time being, to enforce premarket review and quality system regulations against manufacturers that develop and perform certain types of LDTs, including "traditional" LDTs and those for rare diseases and "unmet needs."[142]

In the second draft guidance document, the FDA described the process by which laboratories should notify the agency with regard to the development of new LDTs and existing LDTs involving significant changes.[143] Under the draft guidance, LDT developers would be subject to registration and reporting requirements similar to those applicable to other device manufacturers.

Several legal challenges to the FDA's proposed regulation of LDTs are in the works--and the FDA continues to collect critical comments from many industry participants.[144]

5. Medical Device Data Systems

In June, the FDA issued draft guidance concerning the agency's approach to certain types of hardware and software "that transfer, store, convert formats, and display medical device data or medical imaging data."[145] Noting its "additional experience with these types of technologies," the FDA has determined that "these devices pose a low risk to the public."[146] For those devices that fall into the defined categories of medical device data systems, medical image storage devices, and medical image communications devices, the FDA "does not intend to enforce compliance with the regulatory controls, including registration and listing, premarket review, post-market reporting and quality system regulation . . . ."[147] Further, the FDA announced proposed edits to the current (as of September 2013) version of its "Mobile Medical Applications" policy, which would conform more closely to the policy announced in the new guidance.[148]

6. Nanotechnology

Recognizing the increased role of nanotechnology in health care products, the FDA this year released guidance documents with respect to nanotechnology. The agency did not release specific guidance on nanotechnology as it relates to medical devices, but instead released general guidance that "describes FDA's thinking on determining whether FDA-regulated products involve the application of nanotechnology."[149] Specifically, the FDA stated in the guidance that it will consider two factors when considering whether an FDA-regulated product involves nanotechnology:

- Whether a material or end product is engineered to have at least one external dimension, or an internal or surface structure, in the nanoscale range (approximately 1 nm to 100 nm); [and]

- Whether a material or end product is engineered to exhibit properties or phenomena, including physical or chemical properties or biological effects, that are attributable to its dimension(s), even if these dimensions fall outside the nanoscale range, up to one micrometer (1,000 nm).[150]

While the ultimate effect of this general guidance on FDA-regulated medical devices is left unclear, the FDA suggests that "[a]n affirmative finding to either of [these two questions] . . . might suggest the need for particular attention to the product by FDA and/or industry for potential implications for safety, effectiveness, public health impact, or regulatory status of the product."[151]

C. Case Law Developments: Courts Reject FDA's Positions on Device Issues

In two notable decisions this year, the FDA saw federal courts reject the agency's views on the scope of its "inherent authority" and the dividing line between a drug and a device.

First, in *Ivy Sports Med., LLC v. Burwell*, a divided panel of the D.C. Circuit rejected the FDA's argument that the agency had "inherent authority" to reclassify a device from Class II to Class III and rescind the device's 510(k) clearance.[152] According to the D.C. Circuit, where "Congress has spoken[,]" an agency's "inherent reconsideration authority does not apply . . . ."[153] Given that

Congress has enacted a procedure for FDA to reclassify devices,[154] the FDA was not permitted to "short-circuit or end-run the carefully prescribed statutory reclassification process. . . ."[155]

Further, in a long-running dispute between French medical device maker Prevor and the FDA related to Diphoterine® Skin Wash ("DSW"), Prevor notched its second victory in an effort to have the FDA regulate its product as a device rather than a drug. In 2012, the U.S. District Court for the District of Columbia had held that the FDA had improperly determined that DSW, a pressurized canister that uses a liquid substance to wash harmful chemicals away from skin, was a drug for the purposes of regulation[156]--a determination that could have had expensive consequences for Prevor. The FDA went back to the drawing board, and again determined that DSW is a drug and not a device.[157] In September, upon considering the FDA's new contentions, the same court held that the "FDA hardly changed its reading of the statute [it used to justify the determination] and relied on an arbitrary standard that contravenes the plain meaning of the law."[158]

At issue was whether the FDA properly interpreted statutes and regulations providing that a medical product's status as a drug or a device depends on its "primary mode of action," which in turn is defined as the mode of action "expected to make the greatest contribution to the overall intended therapeutic effects" of the product.[159] DSW was defined in the record as achieving its purpose using a physical and mechanical mode of action to achieve 90% of its overall effect, and a chemical mode of action to achieve 10% of its overall effect.[160] The FDA had interpreted the statute and regulations to mean that a product should be regulated as a drug if the chemical effect "meaningfully contributes to" the product's effect.[161] Using a *Chevron* analysis, the court held that the plain meaning of "achieve" in the relevant statute unambiguously *did not* equate to "meaningfully contributes to."[162] The court further held that, even if the statute was ambiguous as to the meaning of "achieve," the FDA's interpretation of the statute was unreasonable because the "FDA provides no other rationale [other than a need to 'render classification decisions early and quickly'] for imposing this new standard."[163] The court denied the FDA's motion for summary judgment on the issue and remanded the issue to the FDA for further consideration.[164] Notably, however, the court left open the possibility that the FDA could classify DSW as a drug-device combination product, provided that it also "adopts a plausible construction of the relevant statutory language."[165]

V. Anti-Kickback Statute

The AKS prohibits companies and individuals from offering, paying, soliciting, or receiving "remuneration" to induce or reward referrals of business that will be paid for by Medicare, Medicaid or other federal health care programs.[166] The government has interpreted the term "remuneration" "to cover the transferring of anything of value in any form or manner whatsoever."[167] By violating the AKS, an entity or individual may also violate the civil monetary penalties law and the FCA.[168]

During the past year, several AKS-related developments were notable for pharmaceutical companies and medical device manufacturers. Those developments, described below, include: the launch of new reporting requirements for companies who make payments to physicians or hospitals; proposed regulations that expand safe harbors available under the AKS; and several settlements that serve as reminders of just how complicated it can be to comply with the AKS.

A. Open Payments Database Comes Online, Requiring Companies to Self-Report Payments Made to Health Care Providers

The second half of 2014 saw the long-awaited launch of the "Open Payments" database, which tracks payments made by drug and device companies (among others) to physicians and teaching hospitals. Regulations promulgated under the Physician Payments Sunshine Act provisions of the PPACA require drug and device companies to self-report annually any payments made to a physician or teaching hospital.[169] Those payments, ranging from multimillion dollar grants to eleven-dollar plates of pasta, are cataloged in a searchable database available to the public online.[170]

The Centers for Medicare and Medicaid Services ("CMS") released the first round of data, encompassing payments from August through December 2013, in September 2014. The data offered a glimpse into the breadth and scope of payments made by drug and device companies. All told, the first report showed that almost 1,400 companies made nearly 4.4 million payments totaling approximately $3.5 billion to more than 545,000 physicians and teaching hospitals.[171] Notably, the publicly released data does not include details regarding many of those payments. Under the regulations, if payments are made in connection with research and development or clinical trials, publication of those payments can be delayed for up to four years to help protect sensitive business information.[172] The CMS data shows that companies are making good use of that provision: companies have sought delayed publication for at least 190,000 payments worth more than $550 million.[173]

With the reporting requirements now in place, companies can expect that the government will be closely monitoring their compliance with the regulations in 2015 and beyond. Penalties for violations of the reporting requirements--even for unintentional mistakes--can be stiff: up to $10,000 for each payment that is not reported timely, accurately, or completely, with an annual maximum of $150,000; and up to $100,000 for each instance where a company "knowingly fails to timely, accurately or completely report the information required in accordance with the rules . . . ," with an annual maximum of one million dollars.[174]

Companies also can expect that the government and potential *qui tam* relators will sift through the payment data to identify potential AKS violations, which may have resulted in the submission of false claims that trigger liability under the FCA.[175] Although CMS recognizes that "[d]isclosure of the financial relationships between the medical industry and healthcare providers is not intended to signify an inappropriate relationship,"[176] drug and device companies can safely assume that the government and potential relators will take a hard look at the data.

B. New Proposed Regulations Add Additional Safe Harbors from Anti-Kickback Statute Liability

In October, HHS OIG published a proposed rule that would create additional safe harbors to the AKS.[177] Safe harbors have existed under the AKS since 1991,[178] but the PPACA and other recent laws have necessitated updates to the existing regulations. As in the past, HHS OIG intended the new and revamped safe harbors "to limit the reach of the [AKS] somewhat by permitting certain non-abusive arrangements, while encouraging beneficial or innocuous arrangements."[179]

For pharmaceutical companies in particular, the most significant change is the codification of a new PPACA safe harbor for discounts provided by pharmaceutical manufacturers under the Medicare Part D Coverage Gap Discount Program. Under the proposed rule, pharmaceutical companies that participate in and fully comply with the requirements of the Coverage Gap Discount Program would be permitted to offer discounts on certain drugs to certain beneficiaries at the point of sale.[180] Other important changes include a proposed rule that would allow Medicare Part D plan sponsors to waive an enrollee's copayment requirement for the first fill of a generic drug.[181] As HHS OIG noted, these waivers are "designed to minimize drug costs by encouraging the use of lower cost generic drugs."[182]

But the proposed regulations are more sweeping when it comes to how health care providers work together to control costs and create savings, including: (1) provisions that would protect certain cost-sharing waivers for pharmacies and medical transport companies; (2) an amended definition of "remuneration" in the Civil Monetary Penalties regulations at 42 C.F.R. § 1003; and (3) a "gainsharing" rule that would permit hospitals to offer incentives for reduced or limited services (if certain safeguards are in place).[183] These new regulations, if they become final, could have far-reaching effects on the types of incentives and discounts that are permissible under the AKS.

The proposed rule attracted more than 100 comments from organizations and individuals, and there may be significant changes before HHS OIG promulgates the final rule. But overall, the proposed regulations seem to recognize that health care policy is changing in fundamental ways and therefore adopt a more nuanced approach to fraud and abuse enforcement in federal health care programs.

C. Two HHS OIG Opinions Offer Examples of Programs that Trigger Anti-Kickback Scrutiny

In April, HHS OIG issued an advisory opinion indicating that a laboratory testing company would potentially violate the AKS and the civil anti-kickback statute by paying an electronic health records ("EHR") vendor a fee each time a physician opted to use the laboratory testing company's services based on a request through the EHR vendor's interface.[184] Under the arrangement at issue, the EHR vendor integrated laboratory results into physicians' EHR systems and also allowed physicians to transmit lab orders.[185] When a physician sought to order laboratory work, the EHR vendor either charged the physician a fee (if the laboratory offering the tests was "out of network") or assessed the laboratory a fee (if the laboratory was "in network"). Thus, by paying a per-transaction fee directly to the EHR vendor, the laboratory testing company became an "in network" provider of laboratory tests, such that physicians did not have to pay any fee to use the EHR vendor's application when they ordered tests.[186] HHS OIG recognized the very minimal incentive this arrangement likely offered to physicians and also recognized the value of having laboratory tests seamlessly integrated into electronic health records.[187] Nevertheless, HHS OIG determined that the arrangement allowed the laboratory company "to pay compensation to the Referring Physicians, by relieving them of a financial obligation, in return for the Referring Physicians' laboratory test referrals."[188] Thus, HHS OIG advised that the arrangement likely violated the AKS.[189]

In July, HHS OIG issued another advisory opinion, but this time with a more industry-friendly outcome.[190] HHS OIG considered an arrangement whereby a drug company partnered with an online retail pharmacy to make its brand-name drug available at a discount directly to consumers who had a valid prescription.[191] Although the drug was eligible for coverage under Medicare Part D, most third-party formularies did not cover it in practice (and instead covered only generic equivalents); most payors placed restrictions on coverage and/or reimbursement for the drug.[192]

HHS OIG recognized concerns over whether providing a discounted price for the brand-name drug could incentivize consumers to buy the drug and then eventually switch over to having it covered by a federally funded program, as well as concerns that the company could use the discount to incentivize customers to request other products manufactured by the drug company that *were* reimbursable by the government.[193] And the OIG also considered whether offering a discount and partnering with the online pharmacy would create an opportunity for the pharmacy to cross-sell other products for which payment would be made by the government.[194]

Ultimately, however, the OIG concluded that it would not take action against the company in connection with the arrangement.[195] In reaching this conclusion, the OIG focused on the fact that the arrangement was limited to a single drug and that there were specific restrictions in place to prevent cross-marketing of other products or services by the drug company or the online pharmacy.[196] The OIG also noted there was a low risk that the discount would ever induce customers to start taking the drug before eventually seeking federal reimbursement; notably, there were significantly cheaper generic alternatives and coverage of the brand-name drug by any federally funded program was extremely limited.[197]

Taken together, these opinions are reminders that compliance with the AKS and the civil monetary penalties anti-kickback law requires highly fact-intensive analyses, and nearly every incentive, discount, and third-party agreement in the health care industry may raise the specter of a kickback arrangement.

D. Federal Regulators Continue Their Aggressive Enforcement of the Anti-Kickback Statute and Related Laws

The DOJ notched several AKS-related settlements with device and pharmaceutical companies during 2014. For example, a U.S. drug company and its subsidiary agreed to pay $27.6 million in connection with an alleged scheme to pay a physician to prescribe an antipsychotic medication.[198] The physician became the nation's leading prescriber of the drug and allegedly received a lucrative "consulting agreement" and other benefits in exchange (including all-expenses-paid trips to Miami for both the physician and his wife).[199] The DOJ touted the settlement as yet another achievement of the Health Care Fraud Prevention and Enforcement Action Team initiative, a strike force including representatives from the DOJ and HHS.[200]

In January, a California-based drug company paid $40.1 million to settle FCA claims that hinged on alleged violations of the AKS and off-label promotion.[201] According to the government, the company paid more than $11.5 million to a doctor who served as chair of a non-profit organization that

endorsed standardized health care practices. The company allegedly made the payments in hopes of persuading the doctor to recommend the company's product for the preparation of a patient's skin before surgery or injection.

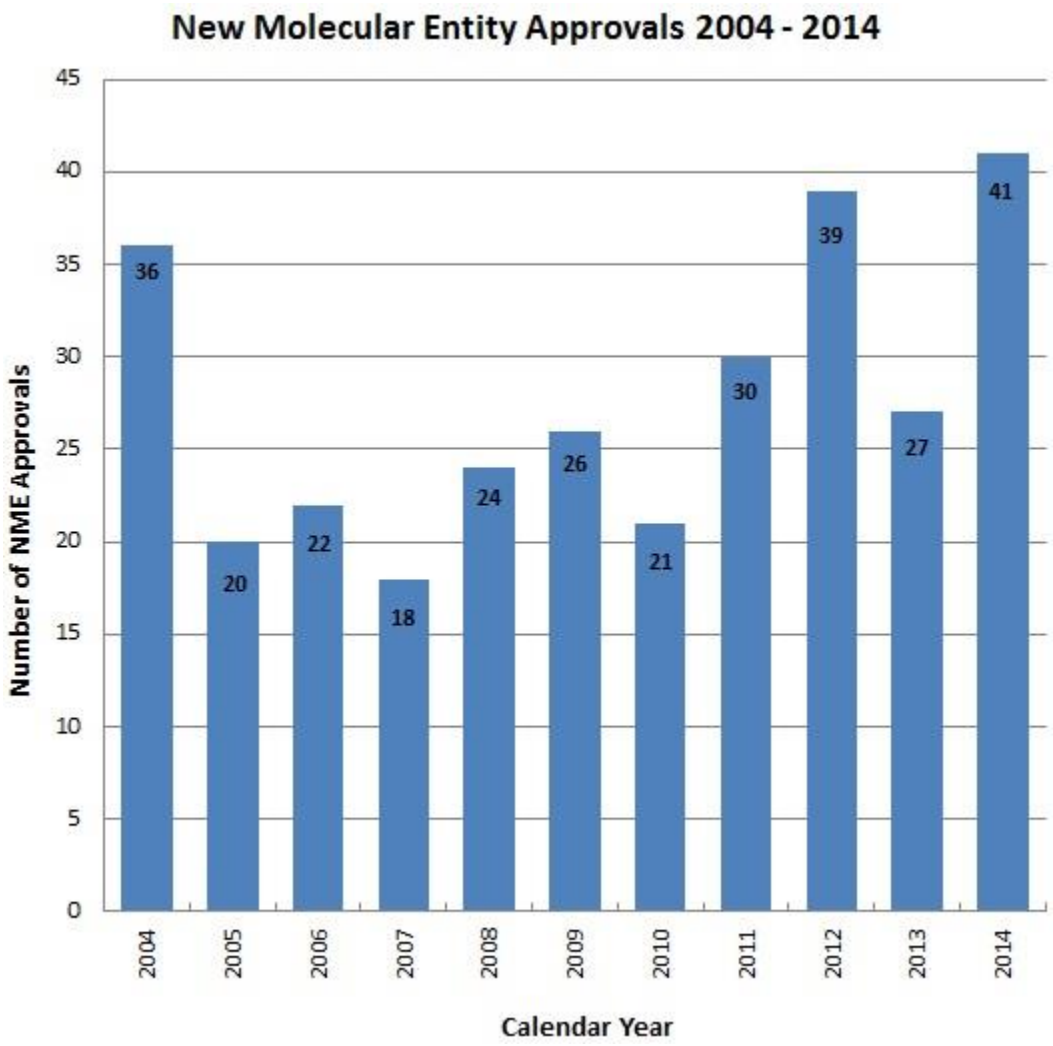
In May, a device company agreed to pay $9.9 million to resolve FCA claims premised on kickbacks that the company allegedly paid to induce physicians to use its pacemakers and defibrillators. According to the government, the company paid physicians to speak at events that were directed at generating referrals, provided free business and marketing plans to the physicians, and gave the physicians tickets to sporting events.[202]

In October, a device company agreed to pay $6.07 million in connection with allegations that it paid members of physicians' staffs to influence the physicians to order its bone growth stimulators.[203] The company allegedly provided the payments to the staff members under personal services agreements, but the government did not explain how the agreements failed to fall within the personal services safe harbor codified at 42 C.F.R. § 1001.952(d).[204]

Several other companies reached smaller AKS-related settlements with the government during the course of the year.[205] Meanwhile, HHS OIG had a less active year enforcing the civil monetary penalties law's anti-kickback provision against drug and device companies. Of note, in August 2014, a distributor for medical device manufacturer Zimmer, Inc., agreed to settle an enforcement action alleging that the distributor paid kickbacks--through independent contractors--to third parties to induce them to recommend Zimmer products to physicians in Florida. The distributor contested the allegations, but nevertheless agreed to pay $123,000 as part of the settlement.

VI. Drug Development and Clinical Trials

The past year saw *forty-one* new drug approvals--the most in eighteen years and the second-highest in history.[206]



Source: U.S. Food & Drug Admin., Ctr. for Drug Eval. & Research

In addition to the sheer quantity of approval activity, other 2014 developments demonstrated the government's serious commitment to improving clinical trials and getting more products to patients more quickly. In May, the FDA announced its plan to allocate as much as $37.5 million over the next five years to aid the Clinical Trials Transformation Initiative in its goal to increase the quality and efficiency of clinical trials.[207] And in an October 29, 2014 Federal Register notice, the FDA requested industry and other public comment on "best practices for communication between FDA and investigational new drug application sponsors during drug development."[208] These comments will aid the FDA in creating draft guidance to further improve the efficiency of clinical trials. Indeed, 2014 saw quite a bit of guidance activity and several pieces of proposed legislation on that front.

A. Finalized Guidance on Improving Clinical Trials

In 2014, the FDA finalized two guidance documents geared toward improving the quality and efficiency of clinical trials:

- **IDE Clinical Investigations Guidance:** On August 19, 2014, the FDA published its final guidance, "FDA Decisions for Investigational Device Exemption Clinical Investigations," a draft of which was issued on June 14, 2013.[209] After evaluating an IDE application, the FDA regulations provide for three possible actions: Approval, Approval with Conditions, or Disapproval.[210] This guidance was developed to provide clarity regarding the FDA's IDE decision-making and communications regarding applications.[211] Notably, in the final guidance document, the FDA removed the pre-decisional IDE process proposed in the 2013 draft. Although this pre-decisional IDE process was intended to provide sponsors more timely feedback and allow for quicker resolution of issues,[212] the FDA ultimately rejected it, noting that some commenters were concerned that the process itself would be too time- and resource-consuming.[213]

- **Guidance on Clinical Trial Subject Demographics:** On August 20, 2013, the FDA released an action plan to be carried out over the next five years, aimed at bolstering demographic diversity in clinical trials, including race/ethnicity, sex, and age.[214] This report, which was generated in response to Congress's directive in Section 907 of FDASIA, contains "27 responsive and pragmatic actions, which are divided into three overarching priorities: improving the completeness and quality of demographic subgroup data collection, reporting and analysis (quality); identifying barriers to subgroup enrollment in clinical trials and employing strategies to encourage greater participation (participation); and making demographic subgroups data more available and transparent (transparency)."[215] The issue of clinical trial demographics has come into the spotlight with the globalization of research and the growing interest in personalized medicine. Relatedly, the following day, the FDA issued updated draft guidance on sex-specific data in studies of medical devices.[216]

B. Developments in Biosimilar Approval Pathway Regime

One of the government's controversial initiatives to get more drugs to market is the approval pathway for biosimilars put into place by the Biologics Price Competition and Innovation Act ("BPCIA"), which was signed into law as part of the PPACA. The BPCIA allows for an "abbreviated licensure pathway for biological products that are demonstrated to be 'biosimilar' to or 'interchangeable' with an FDA-licensed biological product."[217] The law explains that "a biological product may be demonstrated to be 'biosimilar' if data show that, among other things, the product is 'highly similar' to an already-approved biological product."[218] With the first applications under this pathway, several important guidance releases, and even public debate about how to name biosimilars,[219] 2014 proved to be an important year for biosimilars.

In July 2014, the industry received news of a landmark event: the FDA's acceptance of the first biosimilar application over four years after the BPCIA was signed into law. Sandoz filed the

application for its product Zarxio, a biosimilar version of filgrastim, Amgen Inc.'s Neupogen.[220] The application served as a sign of things to come; in August 2014, Celltrion Inc. filed an application for its product Remsima, a biosimilar of infliximab, Johnson & Johnson's Remicade.[221] Most recently, on December 17, 2014, Apotex Inc. announced that the FDA is reviewing its copycat of pegfilgrastim, Amgen Inc.'s biologic Neulasta.[222] It now appears likely that the first approval could be announced in early 2015; on January 7, 2015, an FDA advisory panel voted unanimously to endorse approval of Zarxio, finding that it meets the similarity standards.[223]

Since passage of the BPCIA, the FDA has issued extensive--though arguably insufficient--guidance to support this new approval pathway, and the agency continued that effort in 2014 with the issuance of two new biosimilar draft guidance documents, "Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product"[224] ("Clinical Pharmacology Guidance") and "Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act"[225] ("Exclusivity Guidance"). The draft Clinical Pharmacology Guidance and the draft Exclusivity Guidance add onto the other six FDA-issued guidance documents relating to biosimilars and/or referencing biological products.

- **Clinical Pharmacology Guidance:** Clinical pharmacology studies are central to demonstrating biosimilarity to a reference product. Building on the FDA's previously issued guidance, the draft Clinical Pharmacology Guidance provides further detail on the clinical showing necessary to demonstrate biosimilarity. As with the FDA's prior draft guidance in 2012,[226] the 2014 draft reiterates a "stepwise" approach to developing clinical data.[227] The guidance articulates a stepwise assessment of biosimilarity, including conducting extensive and comparative structural and functional studies to assess whether the proposed biosimilar product and the reference product can be deemed highly similar, including structural analyses, functional assays, animal data, and clinical study data.[228] The draft guidance provides four possible assessments of biosimilarity: highly similar with fingerprint-like similarity, highly similar, similar, and not similar.[229] It is not entirely clear how these vague categories of "similarity" will be defined, however, and this point generated extensive opposition in industry comments to the draft guidance.[230] Given the centrality of this issue to the biosimilar pathway, hopefully the FDA will provide further clarity in a future update.

This past year also saw the opening of the biosimilar pipeline, although this has hardly diminished the debate over how this area of drug development will evolve. The commencement of a new approval pathway, with multibillion-dollar implications, has the industry watching closely for how the agency treats these initial applications and how policies outlined in FDA guidance documents are applied in practice.

C. Proposed Legislation

With the change in control of the Senate and the bolstering of the majority in the House in the 2014 elections, it is unclear what the new Congress's agenda will be with respect to clinical trial issues. However, Congress did show a strong interest in 2014 in improving clinical trials and increasing drug choice and accessibility through various means:

- **Expanded Access (H.R. 5805):** One area that has been the topic of public debate is expanded access, particularly in light of the recent state laws permitting manufacturers to provide patients with investigational drugs on an emergency basis,[231] bypassing the FDA's expanded access process. Introduced in December 2014, H.R. 5805 includes a provision directing companies to present the FDA and patients with more information regarding how they handle expanded access requests.[232] Other major provisions include requiring sponsors to file expanded-use policies for "covered breakthrough drugs" and requiring them to provide written notice of request denials.[233]

- **Increased Data Exclusivity to Address Unmet Needs:** Introduced on December 18, 2014, the Dormant Therapies Act would allow drug makers to have an unprecedented fifteen years of data exclusivity for a medicine that meets an unmet medical need.[234] Currently, generic drug makers can be prevented from using the data generated by their brand-name counterparts to obtain regulatory approval to sell copycats for five years for a new chemical entity and twelve years for a biologic. U.S. Senator Orrin Hatch (R-UT), a cosponsor of the bill, stated, "We hope to create a time-certain protection to encourage innovators to capture lost opportunities and bring new and essential products to market for the patients who need them."[235] Critics, however, worry that extending the data exclusivity period could delay lower-cost generics of many drugs, maintaining high prices.[236]

  Relatedly, the Orphan Product Extensions Now Accelerating Cures and Treatments Act of 2014 (H.R. 5750), also called the OPEN Act, would provide for an added six months of exclusivity for approved drugs that are subsequently approved for a rare disease indication.[237]

- **Regulatory Transparency, Patient Access, and Effective Drug Enforcement Act:** Introduced in November, this bipartisan legislation seeks to streamline and increase transparency in the approval process for drugs that fall under the Controlled Substances Act.[238] Specifically, it requires the Drug Enforcement Administration ("DEA") to adhere to a specific timeline to schedule certain controlled substances. Further, it aims to speed development of new therapies by permitting researchers to note on their DEA application that the controlled substance will be used only for purposes of clinical trials.

- **Research for All Act of 2014 (H.R. 4879):** This bill provides for the review and development of policies to ensure that the design and size of clinical trials for products granted expedited approval to treat a serious or life-threatening disease or condition are sufficient to determine the safety and effectiveness for both men and women using subgroup analysis.[239] Moreover, the bill provides for inclusion and separate analysis of both male and female animals, tissues, and cells in basic research carried out and funded by the National Institutes of Health. Other key provisions include amendments authorizing the Secretary of Health and Human Services to support continued operation and expansion of Special Centers of Research on Sex Differences and requiring the Comptroller General to provide Congress with updated versions of specific reports on women in drug research.[240]

- **21st Century Cures Act:** Much activity, including a series of white papers and public hearings, surrounded the proposed 21st Century Cures legislation, a discussion draft of which may be introduced by the House Committee on Energy and Commerce Subcommittee on Health in early 2015.[241] This proposed legislation follows a call to action issued by Congress on May 1, 2014 regarding accelerating the discovery, development, and delivery of new treatments to patients.[242]

  The proposed 21st Century Cures legislation seeks to modernize and streamline the clinical trial process to get new treatments to market for patients, particularly with respect to personalized and digital medicine.[243] The forthcoming draft legislation may propose overhauls to various facets of the drug and device development and approval processes. This effort dovetails with other legislative efforts, such as H.R. 5805 discussed above, to expand patient access to drugs outside of the traditional approval process.

VII. Conclusion

2014 did little to diminish either the specter of significant enforcement actions or the regulatory burden for drug and device companies. In fact, if the DOJ and the FDA follow through on their plans from this past year--and current trends continue--2015 promises to be another extremely active year in both the enforcement and regulatory arenas for drug and device companies. We will continue to monitor the developments and report back to you in due course.

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[1] Press Release, Office of Pub. Affairs, U.S. Dep't of Justice, Justice Department Recovers Nearly $6 Billion from False Claims Act Cases in Fiscal Year 2014 (Nov. 20, 2014) (quoting Joyce R. Branda Assistant Attorney Gen., Civil Div., U.S. Dep't of Justice), http://www.justice.gov/opa/pr/justice-department-recovers-nearly-6-billion-false-claims-act-cases-fiscal-year-2014.

[2] October 1, 2013 through September 30, 2014.

[3] Press Release, Office of Pub. Affairs, U.S. Dep't of Justice, Justice Department Recovers Nearly $6 Billion from False Claims Act Cases in Fiscal Year 2014 (Nov. 20, 2014) (quoting Joyce R. Branda Assistant Attorney Gen., Civil Div., U.S. Dep't of Justice), http://www.justice.gov/opa/pr/justice-department-recovers-nearly-6-billion-false-claims-act-cases-fiscal-year-2014.

[4] Fraud Statistics, U.S. Dep't of Justice (Nov. 20, 2014), http://www.justice.gov/civil/pages/attachments/2014/11/21/fcastats.pdf.

[5] *Id.*

[6] DOJ settled a case against Teva Pharmaceuticals USA Inc. and its subsidiary, IVAX LLC, on March 11, 2014, without filing a complaint. *See* Press Release, Office of Pub. Affairs, U.S. Dep't of Justice, Pharmaceutical Company to Pay $27.6 Million to Settle Allegations Involving False Billings to Federal Health Care Programs (Mar. 11, 2014), http://www.justice.gov/opa/pr/pharmaceutical-

company-pay-276-million-settle-allegations-involving-false-billings-federal. Other settled cases involving pharmaceutical companies include the following: *United States ex rel. Kirk v. CareFusion*, No. 10-2492 (D. Kan. Jan. 9, 2014); *United States ex rel. Ryan v. Endo Pharms. Inc.*, No. 05-cv-3450 (E.D. Pa. Feb. 21, 2014), *United States ex rel. Weathersby, et al. v. Endo Pharms. Inc., et al*, No. 10-cv-2039 (E.D. Pa. Feb. 21, 2014); *United States ex rel. Dhillon v. Endo Pharms.*, No. 11-cv-7767 (ED. Pa. Feb. 21, 2014); *United States ex rel. Smith v. Astellas Pharma*, No. 10-999 (E.D. Pa. Apr. 16, 2014); *United States ex rel. Torres v. Shire Specialty Pharms.*, No. 08-4795 (E.D. Pa. Sept. 24, 2014); *United States ex rel. Hsieh v. Shire PLC*, No. 09-6994 (N.D. Ill. Sept. 24, 2014); *United States ex rel. Fox v. McKesson Corp.*, No. 3:12-cv-00766 (M.D. Tenn. Aug. 8, 2014).

[7] DOJ settled a case against Omni Surgical L.P., doing business as Spine 360, on August 29, 2014, without filing a complaint. Press Release, Office of Pub. Affairs, U.S. Dep't of Justice, Manufacturer of Spinal Devices and Surgeon to Pay United States $2.6 Million to Settle Alleged Kickback Scheme (Aug. 29, 2014) http://www.justice.gov/opa/pr/manufacturer-spinal-devices-and-surgeon-pay-united-states-26-million-settle-alleged-kickback. Other cases settled involving pharmaceutical companies include: *United States ex rel. Sant v. Biotronic, Inc.*, No. 2:09-CV-03617 KJM EFB (E.D. Cal. Nov. 6, 2014); *United States ex rel. John Does v. Regional Home Care d/b/a North Atlantic Medical*, No. 12-CA-11979 (D. Mass. Dec. 1, 2014); *United States ex rel. Yu v. Biomet, Inc.*, No. 09-1731 (D.N.J. Oct. 29, 2014); *United States ex rel. Glenn Schmasow v. EndoGastric Solutions, Inc.*, No. 1:12-cv-00078 (D. Mont. Feb 19, 2014); *United States ex rel. Schroeder v. Medtronic Inc.*, No. 2:09-cv-0279 WBS EJB (E.D. Cal. May 28, 2014); *United States ex rel. DeSalle Bui v. Vascular Solutions, Inc.*, No. A10CA883-SS (W.D. Tex. Jul 28, 2014); *United States ex rel. Gustafson v. Alliant Enterprises LLC*, No. 2:08-cv-07214 (C.D. Cal. March 25, 2014) (Stryker Corp. settlement for $1,050,000 regarding alleged misrepresentation of pricing information for durable medical equipment or "DME").

[8] The two settlements that did not result from whistleblower allegations are the Omni Surgical d/b/a Spine 360 resolution and the Teva Pharmaceuticals & IVAX resolution.

[9] *See* 42 U.S.C. §1320a-7b(g).

[10] 42 U.S.C. § 1320a-7b(b).

[11] Press Release, Office of Pub. Affairs, U.S. Dep't of Justice, Biomet Companies to Pay Over $6 Million to Resolve False Claims Act Allegations Concerning Bone Growth Stimulators (Oct. 29, 2014), http://www.justice.gov/opa/pr/biomet-companies-pay-over-6-million-resolve-false-claims-act-allegations-concerning-bone.

[12] Press Release, Office of Pub. Affairs, U.S. Dep't of Justice, Washington-Based Medical Device Manufacturer to Pay up to $5.25 Million to Settle Allegations of Causing False Billing of Federal Health Care Programs (Feb. 19, 2014), http://www.justice.gov/opa/pr/washington-based-medical-device-manufacturer-pay-525-million-settle-allegations-causing-false.

[13] 745 F.3d 694, 700 (4th Cir. 2014).

[14] No. 05-3895, 2014 WL 14118293, at *1 (D.N.J. Apr. 11, 2014).

[15] 772 F.3d 932, 941-42 (1st Cir. 2014).

[16] 21 U.S.C. § 331(a).

[17] Press Release, Office of Pub. Affairs, U.S. Dep't of Justice, OtisMed Corporation and Former CEO Plead Guilty to Distributing FDA-Rejected Cutting Guides for Knee Replacement Surgeries (Dec. 8, 2014), http://www.justice.gov/opa/pr/otismed-corporation-and-former-ceo-plead-guilty-distributing-fda-rejected-cutting-guides-knee.

[18] Press Release, U.S. Food & Drug Admin., Endo Pharmaceuticals and Endo Health Solutions to Pay $192.7 Million to Resolve Criminal and Civil Liability Relating to Marketing of Prescription Drug Lidoderm for Unapproved Uses (Feb. 21, 2014), http://www.fda.gov/ICECI/CriminalInvestigations/ucm387029.htm.

[19] Press Release, U.S. Food & Drug Admin., United States Files Enforcement Action Against South Dakota Laser Medical Device Distributor (Oct. 24, 2014), http://www.justice.gov/opa/pr/united-states-files-enforcement-action-against-south-dakota-laser-medical-device-distributor.

[20] Press Release, Office of Pub. Affairs, U.S. Dep't of Justice, Justice Department Files Suit Against New Jersey Company for Adulterated and Misbranded Medical Devices (Oct. 3, 2014), http://www.justice.gov/opa/pr/justice-department-files-suit-against-new-jersey-company-adulterated-and-misbranded-medical; *see also* Complaint, *United States v. Pharm. Innovations, Inc.*, No. 2:14-cv-06139-ES-JAD (D.N.J. Oct. 2, 2014).

[21] Press Release, U.S. Food & Drug Admin., FDA Resolves Criminal and Civil Actions Against Main Street Family Pharmacy (Dec. 4, 2014), http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm425800.htm.

[22] *See* Press Release, Office of Pub. Affairs, U.S. Dep't of Justice, Bio-Rad Laboratories Resolves Foreign Corrupt Practices Act Investigation and Agrees to Pay $14.35 Million Penalty (Nov. 3, 2014), http://www.justice.gov/opa/pr/bio-rad-laboratories-resolves-foreign-corrupt-practices-act-investigation-and-agrees-pay-1435.

[23] *In the Matter of Bruker Corp.*, Exchange Act Rel. No. 73835 (Dec. 15, 2014), *available at* http://www.sec.gov/litigation/admin/2014/34-73835.pdf.

[24] Hester Plumridge and Christopher M. Matthews, *FBI Interviews Glaxo Employees*, Wall St. J., July 25, 2014, http://online.wsj.com/articles/fbi-interviews-glaxo-employees-1406319760.

[25] 131 S. Ct. 2653 (2011).

[26] 703 F.3d 149 (2d Cir. 2012).

[27] *Warning Letters 2014: Office of Prescription Drug Promotion*, FDA, here (last updated Jan. 12, 2015).

[28] *Advertising Enforcement Actions Decline to Lowest Point in Five Years*, Drug Industry Daily (Dec. 18, 2014), http://www.fdanews.com/articles/169226-advertising-enforcement-actions-decline-to-lowest-point-in-five-years.

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[62] *Id.* at 928-29.

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[65] *Id.* at 116.

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[84] *Id*. at 702 (*quoting Harrison v. Westinghouse Savannah River Co.*, 176 F.3d 776, 786 (4th Cir. 1999)).

[85] *Id.* at 701 (emphasis in original).

[86] *Id.* at 702.

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[89] *See* United States' Statement of Interest As to Defendants' Motion to Dismiss at 3-4, *United States ex rel. Rostholder v. Omnicare, Inc., et al.*, No. 1:07-cv-01283-CCB (D. Md. Nov. 18, 2011), ECF No. 89.

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[102] *Id.* at 7-10.

[103] *Id.* at 10-11, 17.

[104] *Id.* at 10-11.

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[106] Ctr. for Device and Radiological Health, U.S. Food & Drug Admin., 2014-2015 Strategic Priorities (2014), here.

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[108] *Compliance & Enforcement*, FDA, http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHTransparency/ucm199911.htm (last updated Sept. 29, 2014).

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[110] *See* Ctr. for Devices & Radiological Health, U.S. Food & Drug Admin., 2013 Annual FDA Medical Device Quality System Data, http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHTransparency/UCM416501.pdf (last visited Dec. 20, 2014).

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[133] *See id.*

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[169] *See* 42 C.F.R. § 403.900 *et seq*.

[170] *See* 42 C.F.R. § 403.904(c) (describing information that must be reported regarding payments); *id.* § 403.904(h) (setting de minimis thresholds for reporting); *id.* § 403.908 (detailing requirements for electronic submission of payment data); Ctrs. for Medicare and Medicaid Servs., Open Payments Data Fact Sheet (Oct. 1, 2014), https://www.cms.gov/OpenPayments/Downloads/Fact-Sheet-Sept-30-2014-Published-Data.pdf.

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