GSK Shatters the Settlement Ceiling With Record $3 Billion Off-label Deal

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FDA User Fee Bill Clears Congress With OPDP Guidance Provision Intact

After weeks of gridlock, both houses of Congress recently made concessions to ensure passage of the FDA user fee reauthorization measure, with the House caving on a Senate requirement that the FDA devise guidance on Internet promotion, while the Senate gave up some independent drug review requirements. The Food and Drug Administration Safety and Innovation Act, which tweaks the user fee structure for drugs and devices while clearing the way for user fees on biosimilars and generics, now waits on the president’s expected signature. He has until Sept. 30, when the current user fee legislation expires. The new bill is expected to generate $6 billion in industry payments for expedited marketing approval over the course of the measure’s five-year life cycle. Page 4

Ruling on Health Care Law Leaves Physician Payment Disclosure Alone

While the Supreme Court struggled with many facets of the health care law in its recent, highly publicized ruling on the law’s constitutionality, the physician payment disclosure provision was not among them. In fact, the court’s landmark ruling June 28 to uphold the constitutionality of the bulk of the Patient Protection and Affordable Care Act did not even address the issue. Instead, the court’s 5-4 decision in National Federation of Independent Businesses v. Sebelius focused on the individual mandate and whether the federal government can cut off all Medicaid funding to states that refuse to expand their Medicaid rolls under PPACA. The split ruling said “yes” to the first and “no” to the second. Page 5
GSK Shatters the Settlement Ceiling With $3 Billion Deal Covering Off-label Promotion and Missing Data

Records were made to be broken. Mark McGuire’s home run record? Shattered. The four-minute mile? A memory. Now Pfizer’s nearly three-year record for most expensive off-label settlement — $2.3 billion — has been crushed by British drug maker GlaxoSmithKline (GSK), which recently announced a $3 billion settlement with federal officials covering instances of off-label promotion, unreported safety data and allegations of price tampering.

The global deal, which was announced July 2, covers both criminal and civil penalties for a range of alleged offenses dating as far back as 1994 concerning some 10 drugs, according to a release from the Justice Department. Along with the eye-popping sum of money involved, the company also agreed to plead guilty to three misdemeanor violations of the Federal Food, Drug and Cosmetic Act.

It was finalized three days later in U.S. District Court for the District of Massachusetts, earning GSK three dubious distinctions: the largest off-label settlement ever; the largest health care fraud settlement in history; and the largest payout ever by a pharmaceutical company.

Under the criminal portion of the agreement, GSK will pay $1 billion for marketing two antidepressant drugs off-label and for its failure to report required safety data on a diabetes drug to the FDA. The penalty amount will be comprised of a $956.8 million fine and a further $43.2 million in forfeitures, the release stated. Lastly, the company will plead guilty to two counts of introducing a misbranded drug into interstate commerce and a single count of failing to report safety data.

The off-label charges concern the company’s promotion of Paxil (paroxetine) and Wellbutrin (bupropion) in the late ’90s and early ’00s. According to the criminal information filed in the case (see 1 below), GSK promoted Paxil off-label to under-age patients between April 1998 and August 2003 using a variety of means, including speaker programs and a “misleading journal article that misreported” clinical trial data on the drug’s use in patients under 18. The government also accused the company of withholding two studies that debunked its claims of effectiveness in underage patients.

In the case of Wellbutrin, the company was charged with promoting the antidepressant for multiple off-label uses, including weight loss, addiction, Attention Deficit Hyperactivity Disorder and loss of sexual function. According to the Justice Department, GSK “paid millions of dollars” between January 1999 and December 2003 for physicians to attend conferences where off-label uses of the drug were routinely discussed. The company’s off-label efforts also included use of detailing, “sham advisory boards” and continuing medical education programs.

The failure-to-report charge stems from the company’s failure to turn over required drug safety data on the diabetes drug Avandia (rosiglitazone) between 2001 and 2007. More specifically, the charge contends that GSK withheld data from post-marketing studies and research conducted at the behest of European regulators on the drug’s cardiovascular effects.

The Civil Side

The bulk of GSK’s settlement amount will go toward the civil portion of the agreement, with the company shelling out $2 billion in combined False Claims Act deals, according to the Justice Department. In exchange for the payment, federal and participating state officials agreed to drop investigations into a host of alleged activities, ranging from off-label promotion and kickback deals with physicians to price manipulation.

According to the civil complaint (see 2 below), GSK allegedly promoted two of the three drugs named in the

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[See Settlement Ceiling, p. 3]
criminal complaint — Paxil and Wellbutrin — for unapproved uses, along with three others. The complaint’s accusations for Paxil and Wellbutrin mirror those in the criminal charges, while the case against the asthma drug Advair (fluticasone/salmeterol) concerns its alleged off-label promotion for first-line asthma treatment and chronic obstructive pulmonary disease. The other drugs the company allegedly promoted off label are the anticonvulsant Lamictal (lamotrigine) for psychiatric uses and the nausea drug Zofran (ondansetron) for morning sickness.

The civil settlement also accused the company of using kickback schemes to induce physicians to prescribe these drugs, along with four others: the headache drug Imitrex (sumatripan), the irritable bowel syndrome drug Lotronex (alosetron), the allergy drug Flovent (fluticasone propionate) and the herpes drug Valtrex (valaciclovir).

Under the agreement, GSK will pay more than half the civil settlement amount — $1.04 billion — to settle the off-label and kickback allegations, with $832 million going to the U.S. Treasury and the remainder going to participating states.

Another facet of the civil deal concerns GSK’s alleged misrepresentations to doctors about Avandia’s safety. According to the Justice Department, GSK misled physicians about the drug’s safety profile, “causing false claims to be submitted to federal health care programs,” while also allegedly touting unproven cholesterol benefits and cardiovascular benefits when the drug’s label carries cardiovascular warnings. To settle the accusations, GSK agreed to pay $657 million, $508 million of which will go into federal coffers.

The civil complaint’s final allegation concerns how the company reports its prices for drugs. According to the Justice Department, GSK and its corporate predecessors inflated prices for bundled drug sales reported to the Medicaid Drug Rebate Program between 1994 and 2003. The complaint alleges that GSK offered some bundled drug sales arrangements priced below those offered to the Department of Health and Human Services, in violation of Medicaid requirements that it receive the “best” price available. To resolve the allegations, the company agreed to pay $300 million, with $160.97 million going to the federal government, $118.79 million going to participating states and the remaining $20.24 million to public health service groups that allegedly overpaid for the bundled drugs.

Tackling the ‘Driving Forces’

Along with the money and the criminal charges, GSK also agreed to be bound by a five-year-long corporate integrity agreement (CIA). The Justice Department framed the CIA as imposing “novel” requirements on the company that will fundamentally change “the way it does business, including changing the way its sales force is compensated to remove compensation based on sales goals for territories, “one of the driving forces behind much of the conduct at issue,” the Justice Department alleged.

Under the CIA, bonuses paid to GSK executives can be rescinded if an executive is found to have engaged in “significant misconduct.”

In addition, the company will adopt new transparency programs concerning its research and publication practices (see 3 below).

Administration officials lauded the settlement, with Deputy Attorney General James Cole hailing the deal as “unprecedented in both size and scope,” adding that it “underscores the administration’s firm commitment to … holding accountable those who commit health care fraud.”

See Settlement Ceiling, p. 4
User Fee Bill Clears Congress, Goes to President With Internet Advertising Guidance Provision Intact

After weeks of gridlock, both houses of Congress recently made concessions to ensure passage of the FDA user fee reauthorization measure, with the House caving on a Senate requirement that the FDA devise guidance on Internet promotion, while the Senate gave up some independent drug review requirements.

The Food and Drug Administration Safety and Innovation Act, which tweaks the user fee structure for drugs and devices while clearing the way for user fees on biosimilars and generics, now waits on the president’s expected signature. He has until Sept. 30, when the current user fee legislation expires. The new bill is expected to generate $6 billion in industry payments for expedited marketing approval over the course of the measure’s five-year life cycle (see 1 below).

The House and Senate passed markedly different versions of the legislation back in May (see 2 below), but came to a consensus after weeks of haggling, with the House passing agreed-upon revisions by voice vote on June 20 (see 3 below) and the Senate approving the same changes six days later on a vote of 92-4 (see 4 below). Passage of the legislation — often referred to as the Prescription Drug User Fee Act (PDUFA) V since it is the fifth time the user fees have been approved — was hailed by both Democrats and Republicans as a rare example of cooperation between the two houses of Congress.

One promotional element that appeared in both versions of the bill and made it through conference committee unscathed was a provision in Section 506 of Title IX requiring any drugs granted accelerated approval for “serious or life-threatening conditions” submit marketing materials to the FDA for review 30 days in advance of release, a feature that is consistent with prior versions of the legislation.

The bills includes a means of expedited withdrawal of a product’s approval should the manufacturer distribute “false or misleading promotional materials with respect to the product.”

The Senate’s big takeaway in the realm of drug promotion was a guidance requirement missing from the House’s original version of the bill: a requirement that the FDA craft industry guidance covering online promotion. Section 1122 of Subtitle C, “Guidance Document Regarding Product Promotion Using the Internet” — gives the agency two years from the date of enactment to detail the agency’s policy “regarding the promotion, using the Internet (including social media), of medical products that are regulated.”

At present, the agency’s chief watchdog for drug promotion — the Office of Prescription Drug Promotion — pointedly does not distinguish online media promotions from traditional print and broadcast promotions, applying the same criteria to new media as it does to old media.

While agency officials have been pledging for years to issue a variety of electronic media-focused guidances, the only one that touches on the issue was released at the end of 2011 and addresses only unsolicited requests for off-label information (see 5 below).

Karen Riley, with the FDA’s Office of Public Affairs, declined to comment on the ramifications of the new requirement June 2, stating that, as a rule, the agency does not comment on legislative changes until they are signed into law.

See User Fee, p. 5

Settlement Ceiling (continued from p. 3)

In its own press release on the deal, GSK CEO Andrew Witty stated that the deal “brings to resolution difficult, long-standing matters for GSK,” adding that the company has “fundamentally changed our procedures for compliance, marketing and selling.”

While the settlement agreement reveals many new details of the company’s alleged misconduct, the broad strokes of the deal have been widely known for months. GSK disclosed the expected terms of the settlement in its annual report last November, setting aside $3 billion to cover the costs (see 4 below).

For More Information


High Court’s Landmark Health Care Ruling Leaves Physician Payment Transparency Requirement Alone

While the Supreme Court struggled with many facets of the health care law in its recent, highly publicized ruling on the law’s constitutionality, the physician payment disclosure provision was not among them. In fact, the court’s landmark ruling June 28 to uphold the constitutionality of the bulk of the Patient Protection and Affordable Care Act (PPACA) did not even address the issue (see 1 below).

Instead, the court’s 5-4 decision in National Federation of Independent Businesses v. Sebelius focused on the individual mandate — the centerpiece of the 2010 law requiring uninsured citizens to purchase health insurance — and whether the federal government can cut off all Medicaid funding to states that refuse to expand their Medicaid rolls under PPACA. The split ruling said “yes” to the first and “no” to the second.

More specifically, the majority — made up of the four liberal members of the court and Chief Justice John Roberts, who penned the majority decision — found that while the individual mandate was an invalid application of the Commerce Clause and the Necessary and Proper Clause to the Constitution, it could be considered a tax, something Congress is well within its rights to impose.

“The Affordable Care Act’s requirement that certain individuals pay a financial penalty for not obtaining health insurance may reasonably be characterized as a tax,” Roberts wrote in the majority opinion. “Because the Constitution permits such a tax, it is not our role to forbid it, or to pass upon its wisdom or fairness.”

However, the court struck down another section of PPACA granting the Secretary of Health and Human Services the right to cut all Medicaid funding for any state that refuses to adopt the program’s expansion under the law.

“The threatened loss of over 10 percent of a state’s overall budget is economic dragooning that leaves the states with no real option but to acquiesce in the Medicaid expansion,” Roberts wrote in a summary of the ruling.

The court addressed this by simply declaring that specific element unconstitutional, rather than the entirety of the law.

Justice Ruth Bader Ginsburg penned a separate, concurring opinion that supported Robert’s conclusions about the mandate constituting a tax, but disagreed with his views concerning the Commerce Clause and the enforceability of Medicaid’s expansion.

The dissent — which was signed by Justices Antonin Scalia, Samuel Alito and Anthony Kennedy — contended that the law was unconstitutional on all counts and made no effort to spare the feelings of the majority, stating: “The [majority opinion of the] court regards its strained statutory interpretation as judicial modesty,” the dissenters wrote. “It is not. It amounts instead to a vast judicial overreaching. It creates a debilitated, inoperable version of health-care regulation that Congress did not enact and the public does not expect.”

Justice Clarence Thomas wrote a short, single-paragraph dissent that agreed with all elements of the main dissenting opinion except for its finding on the Commerce Clause, drawing an even sharper line against its application than found in either the majority opinion or the dissenting opinion.

No Room for the Transparency Provision

None of the opinions addressed PPACA’s Transparency Reports and Reporting of Physician Ownership or Investment Interests subsection, which stirred considerable debate within the medical products community following its passage and in subsequent efforts to implement it (see 2 and 3 below).

The court’s failure to address the topic is hardly a surprise; none of the four suits that were consolidated into the single case tackled the issue and it was never raised during the three days of arguments the court held on the case in March (see 4 below).

For More Information

1. To read the final version of the bill, go to: http://thomas.loc.gov/cgi-bin/bdquery/z?d112:S.3187.
2. See “House and Senate Versions of PDUFA Include Promotional Regulation for Fast Tracking of Life-saving Drugs,” July 2012, p. 2
4. To review Senate activity for that day, go to: http://democrats.senate.gov/2012/06/26/senate-floor-wrap-up-for-tuesday-june-26-2012/.
Study To Examine Impact of Disease Awareness Information When It Appears in Branded Promos

The FDA is looking to study what impact general information about a medical condition can have on consumers when it appears in a branded ad. In a Federal Register notice posted June 20 (see 1 below), the agency detailed plans to conduct the experimental study, which will evaluate consumer perceptions of “disease information in branded promotional material.”

Specifically, the agency wants to know if the use of general information about a medical condition — such as one might find in an unbranded, disease-awareness campaign — placed in a branded promotion for educational purposes could confuse consumers about the drug’s actual effects.

“When broad disease information accompanies or is included in an ad for a specific drug, consumers may mistakenly assume that the drug will address all of the potential consequences of the condition mentioned in the ad by making inferences that go beyond what is explicitly stated in an advertisement,” the notice stated.

The basis for this is previous research suggesting that consumers find disease-awareness information more reliable than traditional branded advertisements and the agency wants to determine if that consumer perception carries over when that content is applied to branded communications.

“If consumers are able to distinguish between disease information and product claims in an ad, then they will not be misled by the inclusion of disease information in a branded ad,” the notice stated. “If consumers are unable to distinguish these two, however, then consumers may be misled into believing that a particular drug is effective against long-term consequences.”

To determine this, the agency plans to recruit 4,650 participants, asking them to evaluate fictional print ads for three different conditions — chronic obstructive pulmonary disease, lymphoma and anemia — and then judging their response.

The agency will make multiple versions of each ad to test the type of disease information being presented and how it is presented in the ad, according to the notice.

“Some participants will see information about the disease that avoids discussion of disease outcomes the drug has not been shown to address,” while “other participants will see disease information that mentions consequences See Study, p. 7

Ruling (continued from p. 5)

This leaves the provision — often referred to as the Sunshine Provision — and its requirement that medical product manufacturers who pay physicians more than a set amount each year disclose the payments, intact.

The Centers for Medicare and Medicaid Services’ efforts to implement the provision over the past year, which have yet to be finalized, are likewise unaffected (see 5 and 6 below). A related guidance from the FDA concerning data disclosure for drug samples also remains in a state of flux, with the agency recently delaying enforcement of the program by six months (see 7 below).

A smaller provision within PPACA obligating the FDA to study the implications of a mandatory drug facts box on promotional labeling and print advertisements was likewise not addressed by the high court (see 8 below).

For More Information

1. To read the court’s ruling, which includes both majority opinions and dissenting opinions in one file, go to: http://www.supremecourt.gov/opinions/11pdf/11-393c3a2.pdf.


OPDP Untitled Letters Target Web Page, Journal Ad

The FDA recently cited two companies over questionable drug promotions, blasting Quintiles for the content of a web page and Watson Pharmaceuticals over claims appearing in a journal ad. Both companies received Untitled Letters from the agency’s Office of Prescription Drug Promotion (OPDP) — its chief enforcer of drug promotional policy — in June, the only ones the office released that month.

June’s enforcement showing from the office follows a trend of limited enforcement action in recent months, with the office issuing two Untitled Letters in April and an Untitled Letter and a Warning Letter in May (see 1 and 2 below). With the year now half over and only 12 letters to show for it, OPDP is on track for an even quieter year in enforcement than 2011, which yielded 30 such letters (see 3 below).

OPDP’s June 7 letter to Quintiles concerned the branded website for the injectable mucositis drug Kepivance (palifermin). Both the website and the drug belong to Swedish Orphan Biovitrum, but Quintiles acts as the company’s agent in the U.S. According to OPDP, the Efficacy page on the Kepivance site omitted important risk information, minimized risk information and included misleading effectiveness claims about the drug (see 4 below).

OPDP’s first complaint was that the page included numerous effectiveness claims about the drug but omitted relevant risk information from the Warnings and Precautions section of the product’s label. The Untitled Letter also noted that the drug carries risks when taken in conjunction with some other drugs, risks that were not mentioned on the web page.

According to the letter, the page did provide a link to the full product information, but that is not an acceptable substitute for providing the information on the same page. The absence of such information “misleadingly suggests that Kepivance is safer than has been demonstrated,” agency officials stated.

Another concern OPDP had was with a series of images, graphs and claims concerning the drug’s benefit to patients suffering from oral mucositis, such as trouble eating, drinking, swallowing or talking. The content ranged from a simple image of a woman eating a watermelon to a study drawn from patient questionnaires, but the “overall implication of these claims and presentations” suggested that Kepivance would improve these functions, the letter stated. However, much of the material was drawn from research that the agency found lacking, such as the patient questionnaires.

“These claims and presentations of treatment benefit for Kepivance require substantial evidence as demonstrated through adequate and well-controlled trials using well-developed instruments that validly and reliably measure the specific concepts at issue,” the letter explained.

OPDP also harped on a series of charts and associated claims suggesting that Kepivance patients would be less reliant on opioid-based pain relievers to address their problems. According to the letter, these claims are drawn from research that used a different end point, and thus, is not considered substantial evidence to support those claims.

For More Information


2. To comment on the proposed study, go to www.regulations.gov and enter docket “FDA–2011–N–0568” in the search field.

Finally, OPDP noted that Quintiles neglected to furnish the agency with a copy of the web page or the required Form FDA-2253 to go along with it.

The office asked the company to remove all violative materials from the web page, provide OPDP with a list of all similarly violative content and to devise a plan to stop distributing such material. As of July 2, the entire web site for Kepivance was off-line.

**Come, Watson! The blame is afoot!**

OPDP’s second letter for the month went to Watson Pharmaceuticals over claims in a journal ad promoting its injectable anemia drug, Nulecit (sodium ferric gluconate). According to the June 7 Untitled Letter, the two-page ad misbranded the drug by making unsubstantiated claims (see 5 below).

The office’s first complaint with the ad concerned a section boasting about the drug’s ability to reduce anemia patients’ dependence on erythropoiesis-stimulating agents (ESA), which are drugs that boost red blood cell production. The ad stated that research showed Nulecit patients saw a 60.2 percent mean reduction in the need for ESAs, but OPDP took issue with that claim, noting that “reduced ESA dose requirements can be due to multiple confounding factors, making it very difficult to identify the specific cause for any reductions in ESA dosing.”

OPDP also found fault with a claim that taking Nulecit in conjunction with ESAs would reduce patient-care costs. The office noted that the claim was based on a 12-week cost evaluation drawn from two separate, six-week studies. “These studies were conducted separately with different designs and cannot be considered as a continuous 12-week treatment period,” the Untitled Letter stated. Additionally, OPDP concluded that because the first study was open label and the second one was observational in nature, neither could be considered valid support of that claim.

Another concern OPDP expressed over the cost-savings claim concerned the economic model on which the claim was based. The letter noted that this model only took into account the cost of the drugs and associated hospitalizations, ignoring other factors in treatment costs, such as drug administration, lab monitoring and adverse events. While the ad included a fine print disclaimer near the bottom of the page to that effect, OPDP found that it was insufficient to “correct the overall misleading impression that all costs associated with sodium ferric gluconate plus ESAs versus ESAs alone have been identified and analyzed.”

OPDP asked Watson to stop distributing the ad, supply the office with a list of all similarly violative content and to come up with a plan to stop the usage of violative material.

**For More Information**


