Reporting Discrepancies May Trigger CMS Sunshine Act Audit

Drugmakers that face multiple disputes with doctors over payments reported to the Centers for Medicaid & Medicare Services (CMS) under the Physician Payment Sunshine Act will likely face an audit by the agency.

Although CMS will not comment on how it intends to enforce compliance with the new law, CMS will probably view disputes and discrepancies as warning signs that a drugmaker does not have adequate reporting systems in place, Lisa Murtha, partner at Dentons law firm, told WDL Nov. 22.

Under the transparency law, doctors and teaching hospitals have 45 days to review and either certify or dispute a manufacturer’s reported payments before the information becomes public. Drugmakers will be notified of any dispute and be offered an opportunity

(See CMS, Page 4)

FDA Relaxing Restrictions on GSK’s Controversial Diabetes Drug Avandia

Three years after placing heavy restrictions on GlaxoSmithKline’s type 2 diabetes drug Avandia, the FDA said Nov. 25 it is relaxing those restrictions in line with its advisers’ recommendations.

The agency will ease the drug’s risk evaluation and mitigation strategy (REMS) requirements, change its labeling, and will no longer need GSK to conduct a postmarket study of the drug comparing Avandia (rosiglitazone) with Actos (pioglitazone).

“Our actions today reflect the most current scientific knowledge about the risks and benefits of this drug,” said CDER Director Janet Woodcock. “Given these new results, our level of concern is considerably reduced; thus, we are requiring the removal of certain prescribing restrictions.”

(See Avandia, Page 6)
Louisiana Crackdown on Pharma Medicare Fraud Nets $88 Million

Twenty-five drugmakers have agreed to pay the state of Louisiana more than $88 million to settle Medicaid and Medicare fraud charges lodged against them as part of the state’s continuing crusade to recover funds improperly paid out to drug companies.

The state has already collected more than $238 million by pursuing lawsuits against drugmakers.

The latest settlement brings to a close the initial 2010 lawsuit filed by Louisiana’s attorney general James Caldwell accusing more than 100 pharmaceutical companies of inflating drug prices in a bid to increase the reimbursements paid to them by Louisiana’s Medicaid program. Caldwell vows to continue prosecutions for overpayments.

These settlements “send a message to companies that they cannot charge the state more for necessary prescription medications than is appropriate,” Louisiana’s secretary of the Department of Health and Hospitals, Kathy Kliebert, said Nov. 20.

She added, “We have no tolerance for fraudulent charges made to the Medicaid program.”

Caldwell filed another case against 38 drugmakers earlier this year, accusing the companies of deceiving its Medicaid agency into paying for unapproved drugs (WDL, Oct. 18). That suit alleges the drugmakers, including Teva, Mylan, Abbott and Actavis, submitted fake national drug codes and false FDA approval information to the state’s Center for Medicare & Medicaid Services and various drug industry reporting services.

Abbott is also one of the 25 companies that agreed to settle the 2010 case, along with Apotex, Eisai, Eli Lilly, Lupin, Novartis, Perrigo, Ranbaxy, Taro, UCB and others.

— Melissa Winn

FDA CALENDAR

Upcoming meetings through Dec. 11:

- Dec. 9: The Gastrointestinal Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee will hold a joint meeting to discuss two BLAs for Entyvio (vedolizumab injection) submitted by Millennium Pharmaceuticals. The first BLA seeks approval of the drug for the treatment of adults with ulcerative colitis. The second proposes to treat certain adults with moderately to severely active Crohn’s disease. Silver Spring, Md.
- Dec. 10: The FDA will hold a public meeting to discuss patient-focused drug development for fibromyalgia. Silver Spring, Md.
- Dec. 11: The Endocrinologic and Metabolic Drugs Advisory Committee will discuss Amylin’s BLA for metreleptin injection for the treatment of metabolic disorders associated with lipodystrophy, including diabetes mellitus and/or hypertriglyceridemia in pediatric and adult patients with inherited or acquired lipodystrophy. Silver Spring, Md.

Comment deadlines through Dec. 12:

- Dec. 2: Comments due on industry guidance Chemistry, Manufacturing, and Controls Postapproval Manufacturing Changes to be Documented in Annual Reports, docket no. FDA-2010-D-0283.
- Dec. 9: Comments due on industry guidance Expedited Programs for Serious Conditions—Drugs and Biologics, docket no. FDA-2013-D-0575-0028.
- Dec. 12: Comments due on draft guidance for industry Bioanalytical Method Validation; Availability, docket no. FDA-2013-D-1020-00.
Amgen’s Next-Generation Heart Drug Enters Phase III with Positive Results

Amgen’s first long-term trial for its next-generation heart drug evolocumab has shown positive results, heating up the race to develop the emerging class of drugs known as PCSK9 inhibitors.

The results from the Phase II extension trial known as OSLER reflect the sponsor’s first full set of long-term data (52 weeks) and come as evolocumab, or AMG 145, pushes into Phase III. Top-line results from four of the 13 trials planned as part of Amgen’s Phase III PROFICIO program are expected to be released early next year, spokeswoman Ashleigh Koss told WDL Nov. 20.

In OSLER, Amgen’s candidate, combined with an unnamed standard of care (SOC), removed low-density lipoprotein cholesterol (LDL-C), or “bad” cholesterol, from the blood in patients with high cholesterol at a rate of 52 percent, the drugmaker said. When compared with SOC, evolocumab did not markedly increase adverse events (81.4 percent versus 73.1 percent in SOC).

In earlier Phase II trials of shorter duration, evolocumab reduced LDL-C by up to 65 percent and was well tolerated by hundreds of enrolled hypercholesterolemic patients, according to Amgen.

The Amgen candidate is one of a number of PCSK9 inhibitors currently under development. Evolocumab catches Amgen up with Roche, Sanofi and Regeneron and their late-stage PCSK9 inhibitors. Pfizer, Bristol-Myers Squibb, Merck and Alnylam Pharmaceuticals have candidates in various stages of early development.

The drugmakers got a break from the FDA earlier this month when the agency clarified its expectations for developers of PCSK9 inhibitors (WDL, Nov. 25). The agency’s regulatory decisions will be based on “the compound’s effects on the entire lipoprotein lipid panel, particularly LDL-cholesterol, its effects on other markers of potential cardiovascular risk … and blood pressure, and any evidence of off-target toxicity,” spokeswoman Lisa Kubaska said.

— Johnathan Rickman

FDA, EMA Approve Novel Hep C Drugs Offering Alternative Treatment Approach

Regulators in the U.S. and EU have paved the way for a new treatment approach to treat chronic hepatitis C, clearing highly anticipated new drugs from Gilead Sciences and Janssen/Medivir.

The FDA Nov. 22 approved Janssen and Medivir’s Olysio (simeprevir), an NS3/4A protease inhibitor, to treat chronic hepatitis C virus (HCV) infection in combination with pegylated interferon and ribavirin in genotype 1 infected adults with compensated liver disease, including cirrhosis. The drug is the first protease inhibitor indicated for the treatment of chronic HCV infection to be approved for once-daily dosing in a combination antiviral regimen, according to the drugmakers.

The drug has the potential to cure chronic HCV, which affects some 3.2 million people in the U.S., said Douglas Dieterich, Mount Sinai School of Medicine and an Olysio clinical investigator. Janssen has developed a patient outreach program called Olysio Support to educate patients and caregivers about the product.

Analysts don’t expect simeprevir to reach blockbuster status, but do predict fast adoption by patients seeking treatment alternatives. Doctors on an FDA advisory panel have praised the drug.

Also on Nov. 22, the European Medicines Agency’s Committee for Medicinal Products for Human Use recommended marketing authorization for Sovaldi (sofosbuvir), Gilead’s Hep C drug candidate proposed to treat chronic HCV in adults in combination with other medicines.

The FDA’s Antiviral Drugs Advisory Committee last month voted unanimously (15-0) that the available data support the drug’s approval. Sofosbuvir has a PDUFA decision date of Dec. 8.

While proposed for use in combination with other agents, both drugs move patients away from interferon-based therapies, which are known to cause serious side effects. — Johnathan Rickman
Comings & Goings

Research and Development at Google’s new biotech outfit Calico will be headed up by former Genentech executive Hal Barron.

Retrophin has hired Maria Beconi, a former manager at Abbott Laboratories, GlaxoSmithKline and Merck, to serve as vice president of preclinical development. The biotech has also named Pfizer’s former regulatory affairs director Ronald Guido as vice president of regulatory affairs.

Enanta Pharmaceuticals has appointed former NovoNordisk executive Bruce Carter to its board of directors. Carter will also serve as a member of the compensation, nominating and corporate governance committees.

CMS, from Page 1

to resolve the dispute within 15 days of the end of the 45-day period. If the dispute remains unresolved, CMS will publicly report the manufacturer’s reported amount, but mark it as disputed.

Discrepancies between amounts reported by the manufacturer and those reported by doctors in conflict-of-interest disclosures to teaching hospitals or research sites can also draw CMS scrutiny, she said.

Drugmakers should notify physicians and teaching hospitals in advance that they intend to report a payment and what the amount will be, Murtha advised, to try to resolve disputes before they reach CMS’ attention.

Pharmaceutical companies should retain receipts for payments, canceled checks or some sort of proof of payment for every amount reported under the Sunshine Act, she added.

Murtha said manufacturers should also have clear policies in place regarding:

- What type of payments can be made and for what purposes;
- Who has the authority to make these payments; and
- What disclosure mechanisms will be used to track and report payments.

Companies should also put an audit response strategy in place now and they should rehearse it, Jennifer Geetter, a partner at McDermott Will & Emery, told WDL. Key personnel should be trained for an audit and a point person should be assigned to respond when any auditor appears on behalf of the government, she said.

Drugmakers must first report data by March 31, 2014. CMS will publish the data on a public website in September 2014 (WDL, Feb. 1). The agency recently published Q&A guidance clarifying aspects of the transparency law (WDL, Nov. 18). — Melissa Winn

FDA FOIA LOG

The FDA received 294 FOIA requests the week of Oct. 21 including the following.


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<tr>
<th>Date</th>
<th>Requester</th>
<th>Requested Information</th>
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<tr>
<td>10/21/2013</td>
<td>Baxter Healthcare</td>
<td>Establishment inspection reports and Form 483s issued to Ipsen Biopharm's United Kingdom facility from September 2012 to 2013.</td>
</tr>
<tr>
<td>10/22/2013</td>
<td>Perrigo</td>
<td>Establishment inspection report from December 2012 to October 2013 for Ohm Laboratories’ Gloversville, N.Y., facility.</td>
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<tr>
<td>10/24/2013</td>
<td>Revogenex</td>
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<tr>
<td>10/24/2013</td>
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<td>NDA for Sanofi’s Nasacort (triamcinolone acetonide).</td>
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<tr>
<td>10/24/2013</td>
<td>Sanofi</td>
<td>Form 483s issued to Novartis’ Liverpool, England, facility.</td>
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FDA Continues Stepped Up Advertising Enforcement with Amgen Untitled Letter

Amgen is the latest drugmaker caught up in the FDA’s recent flurry of enforcement letters for false or misleading promotional materials. An ad developed by the company for its anemia drug Aranesp omitted risks and inflated efficacy claims, the agency says.

The Aranesp (darbepoetin alfa) ad included some risks but failed to disclose the potential for increased mortality, myocardial infarction and stroke in certain patients, the untitled letter posted Nov. 22 states. Amgen directed readers to the full prescribing information for the drug; however, this wasn’t enough to mitigate the omission, the letter adds.

Amgen was also chided for suggesting Aranesp can treat chemotherapy-induced anemia in certain patients with metastatic cancer despite a lack of evidence to prove it.

The FDA also blasted Amgen for claiming the drug will lead to a consistent, controlled rise in hemoglobin in patients. The ad references Aranesp clinical trials, but a rate of hemoglobin rise was not an endpoint in any of the studies, the agency said.

The drugmaker told WDL Nov. 25 it is working to address the agency’s concerns with the ad and other materials that may make similar statements.

The letter to Amgen is the seventh advertising enforcement letter issued since Oct. 24. The FDA also recently handed letters to Aegerion, Duchesnay (see story, page 8) and Daiichi Sankyo (WDL, Nov. 18) for similar violations.

The blast of five untitled letters and two warning letters since the end of October comes after a relatively quiet summer that saw three enforcement letters in July and June combined. The agency has issued 20 letters this year, well behind the 28 issued in 2012.

There are no new initiatives or efforts surrounding the FDA’s Office of Prescription Drug Promotion enforcement activities, spokesman Chris Kelly told WDL. However, the 16-day partial government shutdown this fall did impact the office, which wasn’t able to perform enforcement activities or review complaints, Kelly said.


President Barack Obama Signs Track-and-Trace, Compounding Bill

President Barack Obama Nov. 27 signed into law a bill that establishes both a nationwide track-and-trace requirement for prescription drugs and a system of voluntary FDA oversight of compounding pharmacies.

The Drug Quality and Security Act immediately preempts all state track-and-trace measures and puts in place a series of compliance deadlines for drugmakers.

By Jan. 1, 2015, all finished-dose forms of prescription drugs must include a lot-level transaction history that documents each step a product takes from manufacturer to final sale. Manufacturers face the same deadline for establishing a system to quarantine, investigate and validate via the history record a product suspected of being counterfeit, adulterated or stolen (WDL, Nov. 25).

The FDA has until May to issue guidance on how to create the system to identify and handle suspect products.

Another key deadline is November 2017, when manufacturers must affix a product identifier to each package and product case that features a numerical identifier, lot number and expiration date.

By 2023, drugmakers must create an electronic traceability system that identifies products down to the sales-unit level.

The law also establishes a voluntary oversight scheme for compounding pharmacies, ignoring the FDA’s call for a mandatory system to improve compounder quality. FDA must now begin work on how it intends to accept registration from compounders who choose to submit to FDA oversight. — Robert King
Avandia, from Page 1

Earlier this year, a joint panel of FDA advisors recommended easing REMS requirements on Avandia after a readjudicated analysis of GSK’s RECORD trial found the drug did not show increased risk for cardiovascular (CV) events compared with other diabetes drugs (WDL, June 10).

GSK lost marketing authorization for Avandia in many jurisdictions when meta-analysis studies showed it may be responsible for increased CV risk. However, in the U.S., the FDA in 2010 decided to put heavy restrictions on the drug while it underwent an independent readjudication.

Steven Nissen, author of a meta-analysis study of Avandia and cardiologist at the Cleveland Clinic, said the RECORD findings aren’t reliable and that the FDA is trying to “save face” by easing restrictions.

“With regard to the RECORD trial, you can’t reanalyze a trial that was completed and then unblinded years ago and come up with a meaningful answer,” he told WDL. “It’s ludicrous and would never have been permitted for any other pharmaceutical decision.”

Nissen added that the drug, which lost key patents in 2012, has virtually disappeared from market shelves and is unlikely to rebound after the FDA’s Nov. 25 announcement.

GSK has already agreed to pay millions to settle thousands of lawsuits against the drug.

Another outcome of the Avandia case has been the FDA’s requirement that all diabetes drugs undergo CV risk analysis. In light of outcomes from the RECORD trial, several agency advisers have recommended removing the requirement to reduce the burden on sponsors (WDL, Sept. 6). One advisor has even noted that increased cardiovascular risk is a “common denominator” in diabetes patients and determining whether the drug product poses a higher CV risk in such populations is challenging.

— Ferdous Al-Faruque

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FDA Upgrades Approval for Pfizer’s Xalkori

The FDA has granted “regular” approval for Pfizer’s lung cancer drug Xalkori after conditionally approving it in August 2011 under the agency’s accelerated approval program.

The decision was based on data from a multinational, randomized, open-label and active-controlled trial of 347 patients who were treated with either Xalkori (crizotinib) or chemotherapy. Results showed that patients with metastatic non-small cell anaplastic lymphoma kinase-positive lung cancer taking Xalkori survived without progression of disease for an average of 7.7 months — nearly five months longer than patients in the chemotherapy arm.

The European Medicines Agency conditionally approved Xalkori in October 2012.

FDA Approves Bird Flu Vaccine

The FDA Nov. 22 approved the first adjuvanted vaccine for the prevention of H5N1 influenza, otherwise known as avian or bird flu. The vaccine is intended for use in people 18 years of age and older who are at increased risk of exposure to the H5N1 influenza virus.

The vaccine will be added to the National Stockpile for distribution by public health officials, if needed. The Department of Health and Human Services bought the vaccine from its manufacturer, ID Biomedical, a subsidiary of GlaxoSmithKline Biologicals.

The manufacturer will collaborate with the FDA and other U.S. government agencies on plans to collect additional safety and effectiveness data through U.S. government-sponsored studies of the vaccine, in the event that it is used during an H5N1 influenza virus pandemic.

FDA Rejects Amarin’s SPA Appeal

The FDA’s Office of New Drugs has notified Amarin that it is refusing to review the company’s appeal of the agency’s decision to rescind the special protocol assessment (SPA) for the drugmaker’s ANCHOR study of its heart drug Vascepa.

The FDA rejected the appeal on procedural grounds, denying the company’s additional request to meet with high-level officials regarding the appeal, Amarin said in an SEC filing Nov. 21.

Amarin was told it would first need to address the matter at the division level within the agency.

Amarin believes its appeal is “procedurally correct” and plans to continue to pursue the appeal and approval of the Vascepa (icosapent ethyl) sNDA, the drugmaker added.

Amarin is seeking a second indication for Vascepa as a treatment for patients with mixed dyslipidemia at high risk for coronary heart disease and currently taking statins. The drug was first approved in 2012 as an adjunct to diet and exercise to lower triglyceride levels in adults with severe hypertriglyceridemia.

The FDA’s decision to rescind the SPA was based on three separate outcome trials of other heart drug candidates, which the agency said “fail to support the hypothesis that a triglyceride-lowering drug significantly reduces the risk for cardiovascular events” in the intended patient.

EMA OKs Continued Iclusig Availability

EU regulators Nov. 22 assured Ariad that its leukemia drug and sole product Iclusig can continue to be sold throughout Europe for its approved indications.

The positive appraisal of Iclusig (ponatinib) by the European Medicines Agency’s (EMA) Committee for Medicinal Products for Human USP gave Ariad a needed lift after the FDA last month ordered the drug removed from U.S. market shelves. The drug’s risk of life-threatening adverse events, including blood clots and narrowing of blood vessels, has been cited in FDA safety alerts.

In consideration of those concerns, the EMA issued a number of recommendations for the drug, including that it should not be used in patients with a history of heart attack or stroke, unless the benefits of taking the drug are greater than the risks.
Duchesnay Flagged for Omitting Risks of Morning Sickness Drug

Shortly after Duchesnay received FDA approval for its morning sickness drug Diclegis, the agency says the Canadian drugmaker sent a letter to customers touting the drug’s benefits but none of its risks.

The letter failed to mention any warnings, contraindications, precautions or adequate directions for use for Diclegis (doxylamine succinate and pyridoxine hydrochloride), the FDA says in an untitled letter released Nov. 22. The FDA approved the drug in April to treat nausea and vomiting in certain pregnant women (WDL, April 12).

In addition to the risk omission, Duchesnay’s sales letter failed to properly convey that the drug wasn’t studied in women with hyperemesis gravidarum, a rare disorder that can lead to extreme nausea and vomiting in pregnant women, the agency said.

The FDA also knocked Duchesnay for not naming the active ingredient alongside the drug’s brand name, a common issue that drugmakers struggle with (WDL, Nov. 25).

The FDA wants Duchesnay to immediately stop distributing the letter about Diclegis.

The Diclegis sales letter inadvertently omitted the inclusion of a product logo and a footer that included important safety information, none of which has since nor will be disseminated again in the future, Duchesnay spokeswoman Laney Landsman told WDL. “The company is making every effort to comply with all regulatory requirements and has taken affirmative steps to reinforce its commitment to regulatory compliance.”


FDA Seeks More Data on Forest and Gedeon Richter’s Schizophrenia Drug

The FDA has handed Forest Laboratories and Gedeon Richter a complete response letter asking for more data on cariprazine, the companies’ drug candidate to treat schizophrenia and manic or mixed episodes of bipolar I disorder in adults.

The agency affirmed the drug’s efficacy in the treatment of schizophrenia and mania. “We believe this request was made to better define the optimal dosing regimen to maintain the demonstrated efficacy, while minimizing the potential for the development of adverse events,” said Marco Taglietti, president of Forest Research Institute, on Nov. 21.

Cariprazine has been evaluated for the proposed indication in a clinical program involving more than 2,700 patients. The drug, an orally active, potent dopamine D3-preferring D3/D2 receptor partial agonist, is also under development as an adjunct treatment for major depressive disorder.

Forest said it plans to meet with the FDA to discuss the complete response letter and determine exactly what additional information and clinical data the agency is looking for. — Lena Freund
Managing Contract Manufacturers and Testing Labs

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