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INSIDE THIS ISSUE

Access to Drug Decisions Led to Insider Trading Charge Against FDA Chemist

An FDA chemist and his son have been charged with insider trading in connection with an alleged multi-million dollar scheme based on FDA regulatory decisions for drugs.

A criminal complaint unsealed by the Department of Justice (DoJ) March 30 charged chemist Cheng Yi Liang and his son, Andrew Liang, with conspiracy to commit securities fraud and wire fraud relating to their trading in the securities of five pharmaceutical companies: Clinical Data, Vanda Pharmaceuticals, Progenics Pharmaceuticals, Middlebrook Pharmaceuticals and Momenta Pharmaceuticals.

The DoJ says the insider trading scheme amounted to $2.27 million in profits. "Cheng Yi Liang was entrusted with privileged information to perform his job of ensuring the health and safety of his fellow citizens," Assistant Attorney General Lanny Breuer said. "According to the

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FDA: No Intention to Act Against Pharmacies Compounding Cheaper Makena

The FDA has clarified its position in regards to pharmacists compounding cheaper versions of KV Pharmaceutical's pre-term birth drug Makena, saying it will not be taking enforcement actions against them.

"FDA understands that the manufacturer of Makena (hydroxyprogesterone caproate), KV Pharmaceutical, has sent letters to pharmacists indicating that FDA will no longer exercise enforcement discretion with regard to compound versions of Makena. This is not correct," the agency said Wednesday.

"In order to support access to this important drug, at this time and under this unique situation, FDA does not intend to take enforcement action against pharmacies that compound hydroxyprogesterone caproate based on a valid prescription for an individually identified patient."

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complaint, he and his son repeatedly violated that trust to line their own pockets."

The elder Liang has had access to the FDA's private internal tracking system for new drug applications, referred to as DAARTS, since 1996 when he became a chemist in the FDA's Office of New Drug Quality Assessment. Liang used DAARTS to view confidential non-public documents referring to upcoming FDA decisions to approve or deny drug applications, the complaint states.

The complaint says starting in November 2007, the Liangs repeatedly used information from DAARTS to trade securities issued by companies with pending drug applications. Trades were made in numerous names and accounts, all linking back to benefit the father and son.

Millions in Profits

The scheme was revealed in January when the HHS Office of the Inspector General installed software on Liang's work computer to collect screen shots of his activities. On Jan. 18, the software captured information showing Liang reviewed DAARTS information on Clinical Data's antidepressant Viibryd (vilazodone HCl) that conveyed the FDA was planning to approve the drug. Within minutes, the Liangs' accounts acquired 48,875 Clinical Data shares before the drug was publicly approved on Jan. 21. After the approval was announced, the Liangs sold their entire Clinical Data stock accumulation for profit of nearly $380,000.

The complaint also alleges the Liangs traded in advance of the May 6, 2009, approval of Vanda's antipsychotic Fanapt (iloperidone). Allegedly, the Liangs made an 800 percent profit amounting to more than $1 million.

DoJ says the money was used to pay personal expenses including car purchases, travel expenses and credit card bills.

The DoJ Criminal Division's Asset Forfeiture and Money Laundering Section (AFMLS) also filed a civil complaint in Maryland for forfeiture of proceeds from and property involved in the insider trading scheme for seven brokerage accounts, two bank accounts and two pieces of real property.

In a related case, the U.S. Securities and Exchange Commission (SEC) also charged Liang with insider trading in advance of FDA drug approval decisions, generating more than $3.6 million in illicit profits and avoided losses.

The SEC says Liang illegally traded in advance of at least 27 public FDA approval announcements for 19 publicly traded companies. In addition to the companies listed by DoJ, SEC says he traded securities for Encysive, Connetics, Cornerstone, Pozen, Anesiva, Pharmacyclics, Spectrum, CV Therapeutics, Adolor, Novadel, EPIX, Santarus, Somaxon and Mannkind.

Liang, the SEC alleges, purchased shares for a profit before 19 positive announcements regarding FDA decisions, shorted stock for a profit before six negative announcements and sold shares to avoid losses before two negative announcements. In the Viibryd case, the SEC alleges it took Liang less than 15 minutes to sell all his Clinical Data shares.

Administrative Leave

The commission counted $1.2 million in checks written from Liang's accounts used to pay credit card companies and $65,000 worth of checks written for car purchases later registered to Liang and his wife.

The DoJ says the investigation into the Liangs' insider trading scheme is ongoing. However, "many government agencies like the FDA routinely possess and generate confidential market-moving information. Federal employees who misappropriate such information to engage in insider trading risk exposing themselves to potential civil and criminal charges for violating the federal securities laws," said Daniel Hawke, chief of the SEC's Market Abuse Unit.

Meanwhile, the FDA is urging employees to cooperate with the ongoing investigation.

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Due Diligence, Randomized Trials Needed for Accelerated Approval

The FDA's accelerated approval program has been successful in making oncology drugs available to patients sooner, but due diligence, completing confirmatory studies and more use of randomized trials are necessary to improve approval times and keep patients safe, according to a recent study by agency scientists and officials.

"Accelerated approval is based on a surrogate endpoint reasonably likely to predict clinical benefit in patients with a serious or life threatening condition," John Johnson, a medical team leader at the FDA and one of the study's authors, told *WDL*. Drugs given accelerated approval must undergo postapproval studies, preferably randomized studies, to confirm clinical benefit, after which accelerated approval can be converted to regular approval. Drugs that do not demonstrate clinical benefit in confirmatory trials lose their approved indication.

Two Main Concerns

The FDA's two main concerns about accelerated approval, initiated in 1992, were that ineffective drugs would be approved and that drugmakers would not conduct due diligence in postmarket studies, according to the study, published in the March 25 issue of the *Journal of the National Cancer Institute (JNCI).*

Almost 20 years later, both those concerns remain. The agency has given accelerated approval to 47 indications for 35 drugs — three of which failed to show efficacy and lost approval. However, it's difficult to ascertain how many ineffective drugs may have been given accelerated approval, as 14 have not completed confirmatory trials and four are still under FDA review.

Due diligence in conducting postapproval trials has also been an issue, with 11 of the 26 approvals taking more than five years to confirm benefit, and five of those drugs taking more than seven years. MedImmune's Ethyol (amifostine) and Wyeth's Mylotarg (gemtuzumab ozogomycin), two of the drugs that lost approval, took 10 years to be withdrawn from the market. The median and mean times between accelerated and regular approval for all oncology products were 3.9 and 4.7 years, respectively.

Lack of due diligence "is a serious concern that has threatened the continuation of the accelerated approval process," the study says. Until recently, the FDA's only tool for sanctioning drugmakers was revocation of the accelerated approval — an option that is not always in the interest of cancer patients, the study notes. However, a provision in the FDA Amendments Act of 2007 gives the agency authority to levy fines of up to $10 million for lack of due diligence in completing studies.

Insufficiently Accelerated

Accelerated approval, like many FDA processes, has been criticized both for being overly cautious and for being "insufficiently accelerated," Susan Ellenberg, a professor of biostatistics at the University of Pennsylvania, writes in an editorial in the same issue of *JNCI.*

Ellenberg offers her own critique, questioning whether the time savings estimated in the study are accurate. "The time to complete a study aimed at achieving regular approval from the start would likely be far shorter than the time under the current scenario to conduct an initial study to achieve accelerated approval plus the time to conduct a confirmatory study," she writes.

An exception would be if the confirmatory study were a continuation of the initial study, Ellenberg says. The study authors also say this would be the most efficient process, and that preferably the trials would be randomized. Panel members at a February advisory committee meeting agreed that randomized, multi-arm trials are most appropriate for postapproval confirmation (*DID*, Feb. 9).

Ellenberg also cites concerns about toxic drugs becoming available under accelerated

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Comings and Goings: Baxter, Aeterna Zentaris, Achaogen

Washington Drug Letter is starting a new feature, Comings and Goings, about industry personnel movements.

Baxter's board of directors has chosen **James Saccaro** as treasurer. Prior to his new role, he was vice president of strategy. Saccaro joined Baxter in 2002 as manager of strategy for the company's biosciences business, and has also served as vice president of financial planning and vice president of finance for Baxter's operations in Europe, the Middle East and Africa.

Aeterna Zentaris has named **Michael Meyers** to its board of directors. Meyers is CEO of Arcoda Capital Management and manages that firm's global healthcare funds. He has also served as director of biotechnology and pharmaceutical investment banking at Merrill Lynch and vice president of health care investment banking at Cowen & Co.

Kenneth Hillian has been appointed chief medical officer at Achaogen. Hillian joins Achaogen after spending 16 years at Genentech, where he served as senior vice president and head of product development, Asia Pacific. Other positions he held at Genentech include vice president of research operations and pathology and vice president of development sciences.

Ashley Bush has joined Adeona Pharmaceuticals' scientific advisory board. Bush heads the oxidation disorders laboratory at the University of Melbourne's Mental Health Research Institute. He is also the recipient of the American Academy of Neurology's Potamkin Prize for Alzheimer's disease research.

Rosetta Genomics CEO **Kenneth Berlin** has stepped down from the company's board of directors. The board has elected former King Pharmaceuticals **Brian Markison** to take his place. Berlin will remain CEO and the move is in accordance with updated Israeli corporate law.

Law firm McDermott Will & Emery has hired **Andrea Bergman** as senior director of legislation and health policy. She will be based in Washington, D.C., and work within the firm's health industry advisory practice group. Prior to joining McDermott, Bergman held senior advocacy positions with PhRMA, Medco Health Solutions and the Blue Cross Blue Shield Association. — Jonathan Block

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"Federal agents are interviewing a number of [Center for Drug Evaluation and Research (CDER)] staff and collecting documents and files. The Agency is cooperating fully with law enforcement officials regarding this matter and I encourage any of you who are contacted to cooperate fully as well," CDER director Janet Woodcock said in an email to all CDER employees.

Liang has been put on administrative leave, FDA spokeswoman Lisa Kubaska told *WDL*.

The SEC's chart tracking the Liangs' profits from illegal trades is available at www.sec.gov/news/press/2011/2011-76-chart.pdf.

The SEC's official complaint is available at www.sec.gov/litigation/complaints/2011/comp21907.pdf. — Molly Cohen

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Accelerated Approval, *from Page 3*

approval. That issue came into the spotlight in December when the FDA recommended removal of the metastatic breast cancer indication Avastin (bevacizumab) had received under accelerated approval (*DID*, Dec. 17, 2010). Genentech, the maker of the drug, has appealed the recommendation and was granted a hearing, scheduled for July (*DID*, Feb. 25).

One issue the study does not address is the cost of accelerated approval. The authors note that FDA reviews are "limited to issues of safety and efficacy" and so the agency has not considered the financial affects of accelerated approval on consumers and taxpayers. — Wilson Peden

Several Factors Point to Increasing Number of Adverse Events Reported

Adverse event reporting is on the rise, according to a recent study, with half of all reports in the FDA's Adverse Event Reporting System (AERS) database stemming from the past 10 years.

Since its 1969 inception, the AERS database has accumulated 2.2 million reports, with 54.8 percent of them reported in the last 10 years, according to study author Sheila Weiss-Smith, who heads the Center for Drug Safety at the University of Maryland School of Pharmacy. The study was published in the March 28 issue of the *Archives of Internal Medicine*.

However, the 1.65 fold increase from the previous decade and 11.3 percent report volume increase from 2000 to 2010 may not be due to more problems from drugs. Instead, Weiss-Smith's findings show increased reporting of adverse events may be partially due to other factors.

New Safety Information

Increased reporting was driven by the release of new safety information for drugs, Weiss-Smith notes in an analysis.

She says recombinant DNA products had the highest report prevalence. Amgen/Pfizer's Enbrel (etanercept), Abbott Laboratories' Humira (adalimumab) and Centocor Ortho Biotech's Remicade (infliximab) — all of which treat autoimmune disorders — were the first, third and fourth treatments, respectively, with the highest number of adverse event reports. These three products are all tumor necrosis factor (TNF) blockers and in 2005, the FDA required all TNF blockers to add a lymphoma warning. That was followed in 2008 by a change in labeling regarding the risk of fungal infections.

The safety alerts spurred a second larger peak in adverse event reporting, Weiss-Smith said, following the typical increase in reports during the first two years after a drug is approved.

Several additional factors account for the increase in adverse event reports, Weiss-Smith told *WDL*. The change in healthcare providers' reports may be linked to people using more medications or more people using medications, which may account for more physicians' visits, especially since the demographic curve is aging, she said. "Additionally, poly-pharmacy, the use of multiple medicines for the same indication, is on the rise," she added.

She also says consumers are very interested or more aware now, in ways they never have been, about adverse events and therefore are reporting more to the FDA.

Influence of Internet, Legal Action

Weiss-Smith says the internet, as well as publicity from legal actions, may also account for the increased number of reports coming from patients, instead of healthcare professionals.

"We used to see a … curve where reports would trickle in so people would suspect things and the numbers of reports would rise and then would dip down as people got used to the drug and knew what reactions to expect," Weiss-Smith said. "Now the FDA has done a number of safety alerts and that has spurred reporting, sometimes reports from a long time ago … and there's quite a shift in how things are coming to the FDA. The FDA has always had many routes for you to submit reports but now with the internet, it's more accessible."

Regardless of the reason, it is clear adverse event reporting is on the rise. In an eight-year period, from 1998 to 2005, serious events reports increased 2.6 fold and reports of deaths increased 2.7 fold.

Overall, adults between the ages of 30 and 64 accounted for one-third of AERS reports. Patients younger than 18 provided 4.4 percent of reports and patients 65 years and older reported 20.1 percent of the adverse events in AERS. Meanwhile, 37.4 percent of reports did not include age. Patients

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CMS Agrees to Reimburse Dendreon's Provenge

The Centers for Medicare and Medicaid Services (CMS) has made its much-awaited decision on national coverage for Dendreon's novel prostate cancer treatment Provenge, but will leave specific coverage decisions to local Medicare contractors.

CMS said Wednesday that since there is no national coverage determination (NCD) for Provenge, local Medicare administrative contractors (MACs) have discretion in determining their own coverage plan.

"While the memo concludes that there is virtually nil evidence at this time to support off-label use, the memo leaves local MACs with flexibility to determine coverage for such use without a need to reconsider an NCD, should future evidence demonstrate improvement in health outcomes in this patient group," Needham analyst Mark Monane said in a Wednesday note. "Currently, Provenge is available to Medicare patients, as all 15 [MACs] have established coverage guidelines for Provenge."

"We view the lack of an outright off-label restriction as positive," Baird analyst Christopher Raymond agreed.

CMS' decision "proposes that the evidence is adequate to conclude that the use of autologous cellular immunotherapy (ACI) treatment – sipuleucel-T; Provenge improves health outcomes for Medicare beneficiaries with asymptomaptic or minimally symptomatic metastatic castrate-resistant prostate cancer, and thus is reasonable and necessary for that indication under … the Social Security Act," according to a decision summary.

CMS is requesting public comments on its proposed determination before they issue a final decision on June 30.

Provenge is administered in three doses, each two weeks apart, at a total cost of $93,000.

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were hospitalized in 42 percent of reports and in 15.1 percent, the patient died.

According to the study, the drugs with the most adverse event reports include AstraZeneca's antipsychotic Seroquel (quetiapine fumarate); Amylin Pharmaceuticals' Byetta (exenatide) for diabetes; Eli Lilly's osteoporosis injectable Forteo (teriparatide); Biogen Idec's multiple sclerosis biologic Avonex (interferon beta 1a); Ortho-McNeil-Janssen Pharmaceuticals' transdermal birth control patch Ortho Evra (norelgestromin and ethinyl estradiol); Bayer's intrauterine birth control device Mirena (levonorgestrel-releasing intrauterine system) and Pfizer's analgesic Vioxx (refecoxib), which was voluntarily withdrawn from the market in 2004 because of an increased risk of serious cardiovascular events.

Weiss-Smith's data analysis is available at archinte.ama-assn.org/cgi/content/extract/171/6/591. — Molly Cohen

J&J to Shake Up Consumer Group, Revamp McNeil

After months of seemingly endless bad news — including product recalls and a consent decree from the FDA — Johnson & Johnson (J&J) is shaking up the organizational structure of its consumer group.

Notably, the company has decided to make its troubled McNeil Consumer Healthcare division part of a separate wing of the company, "in order to give focused attention to quality and compliance," J&J says in an internal memo obtained by *DID*.

J&J's consumer business will be reorganized geographically, which will "simplify the consumer group's structure," and McNeil will become part of a stand-alone OTC division, according to the memo.

Company group chairman Patrick D. Mutchler has been named head of the newly created division, which will comprise J&J's U.S. OTC operations, McNeil Nutritionals, Wellness & Prevention and J&J's joint venture with Merck.

The new corporate structure "will enable quicker reaction to changing market conditions and more efficient execution of region-wide initiatives," the company says.

McNeil has had a rough time lately, having recently signed a consent decree with the FDA that requires the company to complete a lengthy remediation process before it can resume full operations at its Fort Washington, Pa., facility, where many of the recalled drugs were manufactured (*WDL,* March 14).

J&J's corporate shakeup comes to light on the heels of yet another recall, as McNeil announced Tuesday it was recalling an additional lot of Tylenol 8 Hour caplets. McNeil is voluntarily issuing the recall due to "complaints of a musty or moldy odor," but the "risk of adverse medical events is remote," the company says.

McNeil's latest recall follows a recall of almost 43 million bottles of Tylenol 8 Hour, Tylenol Arthritis Pain, Tylenol upper respiratory products, Benadryl and Sinutab that were produced at the Fort Washington plant before it was shuttered (*WDL,* Jan. 24).

J&J and its subsidiaries have also issued recalls for surgical sutures, injection devices and more than 667,000 boxes of its OTC Sudafed.

In addition, J&J subsidiary Ortho-McNeil-Janssen was recently found guilty of making false or inflated claims about the safety and efficacy of its antipsychotic Risperdal (risperidone) by a South Carolina jury (*WDL,* March 28). — Kevin O'Rourke

U.S. Supreme Court Rules Pharma Safe in Purchasing Dispute

The U.S. Supreme Court has ruled a California county cannot sue a group of pharmaceutical companies for allegedly overcharging for prescription drugs covered under their purchasing program.

Santa Clara County, Calif., acting in a class action lawsuit, alleged several big-name drug manufacturers charged more than the Section 340B ceiling price, a program in which participating drugmakers sign pricing agreements and are required to provide statutorily defined discounts on drugs to qualified entities. The program is designed to provide federally funded health clinics with drug discounts.

But the Supreme Court determined in an 8–0 ruling Tuesday that only the U.S. government can enforce its own pricing agreements.

Santa Clara's suit claimed the drugmakers overcharged certain health providers for drugs. The allegations stem from a 2004 report from the HHS' Office of the Inspector General that found in one month in 2002, drug companies overcharged counties and others roughly $41 million.

Defendants in the case included AstraZeneca, Bayer, Bristol-Myers Squibb, GlaxoSmithKline, Merck, Pfizer, Sanofi-Aventis and Takeda.

The Ninth Circuit Court of Appeals reversed a federal district court's decision in 2008 and said the county could sue because it was a direct

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Makena, *from Page 1*

The "unique situation" FDA refers to is the public and political outcry against KV's pricing of Makena, which followed the drug's FDA approval and orphan drug status designation, and subsequent market exclusivity.

Makena is now the first FDA-approved treatment for women to reduce the risk of preterm birth. For years, hydroxyprogesterone caproate was compounded by pharmacists for around $10 to $20 per dose. With the FDA's approval, KV has now set the price of the drug at a reported $1,500 per dose. In response to the price increase, Sen. Sherrod Brown (D-Ohio) requested the company rethink its pricing strategy to make it more affordable, and more accessible, to help reduce preterm births.

In response to public concerns, KV's subsidiary Ther-Rx, which manufactures the drug, initiated a patient assistance program for certain eligible patients. However, Brown was still concerned with holes left in the program's eligibility requirements and, with the support of Sen. Amy Klobuchar (D-Minn.), requested a formal investigation from the FTC into the pricing of Makena (*WDL*, March 28).

FDA Enforcement Discretion

Meanwhile, KV allegedly sent cease-and-desist letters to pharmacists, warning them the FDA would take action if they continued compounding the drug's active ingredients.

In the past, the FDA "has exercised enforcement discretion with respect to most products made through traditional pharmacy compounding," the agency says.

However, in 2006, the FDA sent warning letters to pharmacies with orders to stop distributing compounded anesthetic creams and compounded inhalation drugs (*WDL*, Dec. 18, 2006).

In January, the FDA updated its Compliance Policy Guide Sec. 460.200 on pharmacy compounding to reiterate its stance that drug products compounded by a pharmacist on a customized basis for an individual patient are entitled to exemptions from the Federal Food, Drug, and Cosmetic Act (FDCA). Instead, the FDA will only resort to enforcement action if the scope and nature of a pharmacy's activities raise concerns or result in significant violations of the new drug, adulteration or misbranding provisions of the FDCA.

In Makena's case, the FDA says while greater assurance of safety is provided by an approved product, "under certain conditions, a licensed pharmacist may compound a drug product using ingredients that are components of FDA-approved drugs if the compounding is for an identified individual patient based on a valid prescription for a compounded product that is necessary for that patient."

KV Addressing Concerns

Pharmacists have their own view on the subject. "Of particular concern to [International Academy of Compounding Pharmacists] membership and the physician and patient communities which they serve is whether or not [Makena] can continue to be compounded in light of an FDA-approved product with market exclusivity," said David Miller, IACP executive director.

"There are many reasons why a prescriber would choose a compounded alternative over the FDA-approved product … if a prescriber determines that a compounded preparation of a medication is in the best clinical interest of his or her patient and discusses the available options with a pharmacist, there are no statutory or regulatory prohibitions on that professional decision," he added.

KV says it is addressing concerns over Makena. "We are finalizing solutions to the [pricing] concerns, and will announce them by the end of the week," company spokeswoman Jennifer Forst told *WDL*.

"We share the FDA's long-standing position to ensure that patients have access to FDA-approved medications," she added. "We also believe having available an FDA-approved medication is in the best interest of patients. Makena is closely

(See **Makena,** *Page 10)*

FDA Guidance Concerns Postmarket Requirements, Commitments

A long-awaited final guidance spells out enhanced FDA authority to require postmarket drug and biologics studies and clinical trials and distinguishes between postmarket requirements and commitments.

The guidance "authorizes FDA to require postmarketing studies or clinical trials at the time of approval or after approval if FDA becomes aware of *new safety information*." The new Section 505(o) of the Food, Drug and Cosmetic Act was required by the FDA Amendments Act (FDAAA) of 2007.

The guidance says the FDA may require postmarket studies or clinical trials to assess a known serious risk related to a drug, to assess signals of a risk, or to identify an unexpected risk that available data indicates could be present. These mandatory studies or trials would be postmarketing requirements (PMRs).

Additional studies or trials a company agrees to conduct that do not meet the above conditions would be considered postmarketing commitments (PMCs) and would not be mandatory.

Previously, the FDA used the term PMC to describe all studies and trials conducted after the FDA approved a drug, to gather further information on safety or efficacy. The agency required PMCs only in the case of drugs given accelerated approval, deferred pediatric studies, and animal efficacy rule approvals.

PMCs agreed to before FDAAA that meet the requirements for PMRs will not be converted to requirements unless new safety information emerges, according to the final guidance. As of November, the FDA was still dealing with a backlog of PMCs opened before FDAAA, according to a report commissioned by the agency (*DID*, Nov. 11, 2010).

Examples of studies or trials that would not meet the conditions for a PMR but might be agreed to as a PMC include quality studies with no primary safety endpoint, pharmacoepidemiologic studies to examine the natural history of a disease, and clinical trials whose primary endpoint is designed to further define efficacy.

FDA makes a distinction between the terms "study" and "trial" in Section 505(o)3. Where previously the terms were often used interchangeably, the agency now uses "trial" for research activities in which an investigator assigns a drug or other intervention to patients, whereas the term "study" is reserved for activities such as epidemiological research or lab studies.

The new sections also require drugmakers to provide a timetable for completion and annual status updates on any studies or trials conducted for PMRs and PMCs. PMRs may carry additional reporting requirements at specified milestones.

Companies wishing to appeal a requirement can follow the agency's usual dispute resolution procedures. Under the amendments, failure to conduct a required study or trial can result in misbranding charges, a ban on sales of the drug, or civil monetary penalties of up to $250,000 per violation, for a total of no more than $1 million for a single proceeding.

"Guidance for Industry: "Postmarketing Studies and Clinical Trials" is available at www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM172001.pdf.
— Wilson Peden

CDER Ombudsman Finds Lorcaserin Decision Drew Most Feedback in 2010

Reaction to FDA's rejection of an anti-obesity drug accounted for nearly half of all contacts to the CDER ombudsman in 2010, according to the ombudsman's annual report.

Out of a total of 1,015 contacts, 469 came from consumers and other groups concerned about the Endocrinologic and Metabolic Drugs Advisory Committee's Sept. 16 recommendation not to approve Arena Pharmaceuticals' Lorqess (lorcaserin hydrochloride) tablets for the treatment of obesity. The panel based its recommendation on

(See **Ombudsman**, *Page 12)*

Provenge, *from Page 6*

CMS initiated its review for national coverage last July. The review sparked controversy because such reviews — which determine if the agency adopts a national policy to pay for a product — are uncommon and Provenge's high treatment cost is not supposed to factor into the agency's decision (*WDL*, July 12, 2010).

Government watchdog group Judicial Watch filed a lawsuit against CMS, requesting all of their documents in regards to the review. Sens. Arlen Specter (D-Pa.) and John Kerry (D-Mass.) also joined the fray, sending a letter to CMS Administrator Donald Berwick asking the agency's reasoning for conducting the review.

Provenge became the first immunotherapy for prostate cancer to receive FDA approval last April.

Dendreon said the drug would be available to about 2,000 patients for the year after it was launched and that demand for the drug would exceed supply. The company also said its facilities in Atlanta and Orange County, Calif., would be expanded to run at full capacity.

However, uptake of Provenge may not be smooth, Raymond warns. "Provenge will be the first commercial product launch for Dendreon. While the market appears poised for quick adoption of Provenge, a couple of issues could complicate the launch.

First, its status as the first ACI will require additional education to physician targets. Second, the logistics concerns by physicians may slow uptake given complexity of the Provenge supply chain."

Additionally, future competition could impact Provenge. "While Provenge will enter a market with limited competition at launch, multiple agents are in late-stage trials, some targeting the same patient type or adjacent patient groups. Market approvals of these development agents could impact the size of Provenge's target patient population," Raymond said.
— Molly Cohen

Makena, *from Page 8*

controlled by FDA regulations to monitor safety, efficacy and quality. As an FDA-approved drug, Makena is manufactured in an FDA-regulated and FDA-compliant sterile facility."

Additionally, Forst said Ther-Rx established the Makena Care Connection as a way to make the process of prescribing and obtaining Makena as easy as possible for healthcare providers and patients. It provides "administrative, financial and treatment support for Makena patients in one single point of contact," Forst said. "The Makena Care Connection is actively processing prescriptions for Makena, and is already facilitating access to the financial assistance program for patients in financial need." — Molly Cohen

Purchasing, *from Page 7*

beneficiary of the set pricing agreements. It determined suits like the county's would then spread enforcement burden rather than placing it entirely on the federal government (*WDL*, Sept. 8, 2008).

"Recognizing the County's right to proceed in court could spawn a multitude of dispersed and uncoordinated lawsuits by 340B entities," Justice Ruth Bader Ginsburg wrote in the court's opinion. "With HHS unable to hold the control rein, the risk of conflicting adjudications would be substantial."

The court also notes how HHS doesn't disclose information that could reveal the prices a manufacturer charges for its drugs.

"If Congress meant to leave open the prospect of third-party beneficiary suits by 340B entities, it likely would not have barred the potential suitors from obtaining the very information necessary to determine whether their asserted rights have been violated," the opinion states.

The Supreme Court opinion is available at www.supremecourt.gov/opinions/10pdf/09-1273.pdf. — David Pittman

Generic Labeling Case Splits High Court Justices

Generic drugmakers have no legal responsibility to request a label change on their products even though unlisted adverse events may be known, a lawyer representing generic manufacturers argued before the U.S. Supreme Court.

The high court Wednesday heard the case of *Pliva v. Mensing* to determine if generic drugmakers should be held responsible for inadequacies in labels of their branded counterparts (*WDL*, Dec. 20, 2010).

The case comes after two women alleged they developed a neurological disorder after taking a generic version of Wyeth's gastroesophageal reflux disease drug Reglan (metoclopramide HCl). The court's decision could have wide-ranging implications for future oversight from all drugmakers on their products.

Justices Appear Split

However, during oral arguments Wednesday, justices seemed split as they questioned lawyers for the generic drugmakers, the women and the Justice Department.

Jay Lefkowitz, an attorney for Pliva and Actavis, the companies listed in lawsuits, argued the Hatch-Waxman Act says generic drugs must carry the same warning text as their brand equivalents.

Justice Ruth Bader Ginsburg noted generic makers could propose a revision of a label, even if they are required to carry the same label as the listed drug.

But Lefkowitz maintained companies are under no obligation to ask the FDA for labeling changes.

"There's no question that we could certainly ask the FDA, and in fact if we had reason to believe that a label was not accurate, not strong enough, we would certainly do that," Lefkowitz said. "The question is whether or not there's either a federal obligation or a state duty to do this."

Louis Bograd, the attorney for the two women, argued a label's warnings should be revised as soon as there's reasonable evidence of a serious hazard.

"The government says, and the regulatory structure makes clear, that that provision applies with full force to generic-drug manufacturers, not just to name-brand drug manufacturers," Bograd said.

No Obligation to Notify FDA

Bograd pointed to Section 21 U.S.C. 352(f)(2) that says you can't sell a drug that doesn't have adequate warnings about its risks. Because generic-drug makers must compile information regarding the safety and efficacy of their drug, they have the ability to approach the FDA regarding their products.

"So, when the manufacturer is confronted with information that the warnings on its drug are not adequate, the way it should respond is by immediately going to the FDA and saying to the agency: We have this new information; we ask you, not that we want a different warning from the name brand, but we ask you to approve a stronger warning on both the name-brand product and its generic equivalents," Bograd said.

Although Hatch-Waxman is designed to facilitate the entry of generic drugs into the market, it does "not absolve a manufacturer of his responsibilities after entry onto the market to maintain safety of the drug and the adequacy of the label," Deputy Solicitor General Edwin Kneedler told the court.

Lefkowitz pointed to Title 21, Section 201.57(e) of the Code of Federal Regulations, which deals with the FDA, that says a generic maker "should" notify the agency if it believes there should be a label change. "Not we must, not we shall," he said. "But critically, what the FDA has said is in those situations, we, the FDA, will tell you when the label needs to be changed."

Justices Ginsburg, Elena Kagan and Sonia Sotomayor all questioned Lefkowitz on this argument.

(See **Supreme Court** *Page 12)*

Ombudsman, *from Page 9*

Arena's limited study population and a possible cancer risk seen in animal studies.

The report, released Tuesday, defends FDA's decision, noting that while no toxicologist participated in the panel meeting, a team of FDA toxicology experts had reviewed the Lorqess NDA and related carcinogenicity studies.

CDER's Carcinogenicity Assessment Committee also reviewed the studies and its interpretation was provided at the advisory committee meeting, (*WDL*, Sept. 20).

Arena was issued a complete response letter in October asking for additional clinical and nonclinical data on lorcaserin (*WDL*, Nov. 1).

Overall, consumers, healthcare professionals and advocacy groups accounted for 818 (81 percent) of 2010 contacts with the CDER ombudsman.

Sponsors, consultants, attorneys and whistleblowers made a total of 145 inquiries (14 percent). Of those, 77 percent were from commercial sponsors. Commonly cited concerns included compliance enforcement actions, new drug review delays, questions about the IND and NDA process and illegal promotional activities by competitors.

Many drugmakers also complained that the agency's 13-step electronic submission process, which took effect in June 2009, was confusing and cumbersome.

Fifty-two CDER staffers (5 percent) also contacted the office about workplace conflicts and problems with industry and other constituents.

During 2010, the office broadened its role to include advising on internal regulatory and scientific disputes, in conformance with CDER procedure manuals.

The ombudsman's office also fielded "hundreds" of informal questions about jurisdiction both from within and outside the agency. The office responded to 36 requests for designation and seven requests for reconsideration were handled, most of which related to combination products.

Beginning this year, the report will no longer include queries that are redirected from the ombudsman to CDER's Division of Drug Information.

The report is available at www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ContactCDER/CDEROmbudsman/UCM248815.pdf. — Meg Bryant

Supreme Court, *from Page 11*

"The FDA has said if an ANDA applicant believes new safety information should be added to a product's labeling, presumably because they've gotten information that suggests that the product's labeling is wrong, then it should contact the FDA," Kagan said. "The FDA will determine whether the labeling for the generic and listed drugs should be revised." — David Pittman

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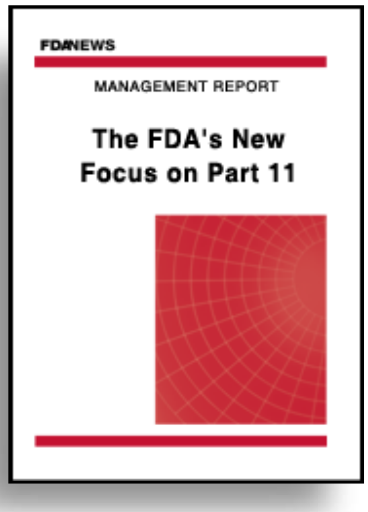

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