TRENDS-in-MEDICINE

November 14, 2010

by Lynne Peterson
and Robin Delgado

Quick Takes

…Highlights from this week's news affecting drugs and devices in development…

SHORT TAKES

- **ARENA PHARMACEUTICALS' Lorqess (lorcaserin)**, a diet drug rejected last month by the FDA over concerns about cardiac safety and preclinical carcinogenicity, did not get any relief from a newly completed study. In a trial in obese diabetics, Lorqess caused valvulopathy in 2.9% of patients, the reason **Wyeth-Ayerst**'s Redux (fenfluramine/phentermine) was pulled from the market in 1997. This study may mean the end of Lorqess.
- **BIOVISTA** signed a pilot research collaboration agreement with **Pfizer** that will use Biovista's technology to help identify new indications for a number of undisclosed Pfizer drugs in development.
- **CELGENE's Vidaza (azacitidine)** was rejected by the U.K.'s National Institute for Health and Clinical Excellence (NICE) as a treatment for patients with high-risk myelodysplastic syndrome (MDS), chronic myelomonocytic leukemia, or acute myeloid leukemia (AML). NICE ruled that the high cost outweighed the benefits in patients ineligible for stem cell transplants.
- **CELSION's ThermoDox (doxorubicin heat sensitive liposomes)** – European regulators granted orphan drug status to this potential liver cancer treatment which is in Phase II development. It already has FDA orphan drug status.
- **CONCEPTUS**, which sells Essure for permanent birth control, is also going to promote **Johnson & Johnson**/Ethicon's Gynecare Thermachoice Uterine Balloon Therapy System, an endometrial ablation product, in the U.S.
- **EDWARDS LIFESCIENCES** received grand-jury subpoenas from the U.S. Attorney's Office for the Central District of California as part of an FDA investigation. The subpoenas sought records related to the Vigilance I Monitor with software release 5.3, a heart function monitor that the company recalled in 2006.
- **ENDO PHARMACEUTICALS' Opana TRF (oxymorphone extended-release)** – The FDA cancelled the planned joint meeting of its Anesthetic and Life Support Drugs Advisory Committee and its Drug Safety and Risk Management Advisory Committee to consider whether Opana TRF should be approved for the relief of moderate-to-severe pain in patients requiring continuous, around-the-clock opioid treatment for an extended period of time. The PDUFA date remains January 7, 2011.
- **Japanese medical device approval process** – Advanced Medical Technology Association (AdvaMed) executives met with Japanese government officials and urged them to expedite approval of medical devices in that country.

Trends-in-Medicine
Stephen Snyder, *Publisher*
2731 N.E. Pinecrest Lakes Blvd.
Jensen Beach, FL 34957
772-334-7409
Fax 772-334-0856
www.trends-in-medicine.com
TrendsInMedicine@aol.com

- **LILLY** is acquiring **Avid Radiopharmaceuticals**, which has an imaging agent (florbetapir) in development to identify the presence of beta-amyloid plaque in the brain to identify and monitor Alzheimer's patients.

- **MCKESSON** – The Hawaiian government filed a lawsuit against McKesson, a drug wholesaler, accusing it of inflating the cost of prescription drugs and "gouging" the state's Medicaid program. Also named in the suit was First DataBank, which compiled prices that the state used in paying for the prescription drugs.

- **MERCK KGaA's Erbitux (cetuximab)** – A study published in ***Lancet Oncology*** found that adding Erbitux to **Lilly**'s Gemzar (gemcitabine) and oxaliplatin appears beneficial in patients with advanced biliary tract cancer. Patients getting the triplet had an overall response rate of 63% and an overall disease control rate of 80%, justifying a large randomized study.

- **NOVARTIS's ASA-404** – Development is being discontinued after preliminary results indicated the drug may not meet the primary endpoint in an ongoing lung cancer trial.

- **OPTIMER PHARMACEUTICALS' Pruvel (prulifloxacin)** – Optimer terminated a small, Phase I study of this experimental infectious diarrhea antibiotic after a larger than expected number of patients developed a rash. Two Phase III trials are already completed, but this Phase I study was at the request of the FDA which reportedly wanted data on the drug's performance in people taking Pruvel + antacids for labeling purposes.

- **ROCHE** is partnering with **Aposense** to use Aposense's EarliTest in its oncology program. The EarliTest uses ML-10, an imaging agent which accumulates in cells undergoing programmed cell death, enabling use of PET (positron emission tomography) to analyze a tumor's response to treatment quickly, perhaps helping to accelerate drug development.

- **Statins** – A retrospective study by the American Cancer Society of >130,000 people over a 10-year period found that long-term use of statins does not increase the risk of cancer of the bladder, breast, colon/rectum, lung, pancreas, prostate, or kidneys. In fact, statin use for ≥5 years was associated with a lower risk of melanoma, endometrial cancer, and non-Hodgkin lymphoma.

- **SUNESIS PHARMACEUTICALS' vosaroxin** – The results of a Phase II trial in AML showed that patients who went into remission after treatment with the drug had median survival of 14.4 months vs. a historical average of <12 months.

- **THORATEC** sold its International Technidyne Corporation (ITC) division, which develops products for hemostasis management and point-of-care testing, to an affiliate of Warburg Pincus.

- **THRESHOLD PHARMACEUTICALS' TH-302** – Results from the 54-patient 403 trial were presented at the Connective Tissue Oncology Society (CTOS) meeting in Paris, showing that this hypoxia-activated prodrug + doxorubicin in soft tissue sarcoma patients naïve to doxorubicin achieved a response rate of 33% and a progression-free survival of 6.4 months. The company is now planning a trial in which the primary endpoint will be overall survival.

- **WATSON PHARMACEUTICALS' Uracyst (chondroitin sulfate sodium)** failed to meet the main goals of a Phase I trial in interstitial cystitis (an inflammation of the bladder wall), and Watson is abandoning development.

- **XOMA's Xoma-052** – Additional results were reported on five patients in a pilot study in uveitis of Behcet's disease, showing that when the patients had a uveitis exacerbation, the patients responded again to retreatment and maintained the response for several months.

NEWS IN BRIEF

Acute Myeloid leukemia (AML) – predictive gene found

A gene – DNA methyltransferase 3A or DNMT3A – has been discovered that can predict the outlook for some patients with AML, according to a report published in the ***New England Journal of Medicine***. Researchers at Washington University School of Medicine in St. Louis, with funding in part from the National Institutes of Health's National Human Genome Research Institute (NHGRI), found the mutation by completely sequencing the genome of a single AML patient and then comparing it to targeted DNA sequencing on ~300 additional AML patients.

The researchers found the DNMT3A mutation in 21% of all AML patients, and those patients had a median survival of only ~1 year vs. ~3.5 years for AML patients without the mutation. The mutations in the DNMT3A gene appear responsible for treatment failure in a significant number of AML patients, a finding which may provide a molecular target against which to develop new drugs. And physicians may start screening for the mutation and adjusting treatment accordingly.

For patients with the DNMT3A mutation, chemotherapy may not be the best first treatment. An investigator, Richard Wilson, PhD, said, "If a patient has a DNMT3A mutation, it

looks like you're going to want to treat very aggressively, perhaps go straight to bone marrow transplantation or a more intensive chemotherapy regimen."

Cheap generic drug programs – affecting quality monitoring

When patients get free generic drugs or pay very low prices for them at Wal-Mart, Target, Walgreens, and other pharmacies, it may help compliance with drug therapy, but it may hurt quality surveillance efforts because those patients are not currently reported to insurers. Instead, the patients may be misclassified as non-users or non-adherers to their medication regimen in the pharmacy claims databases that are used to measure quality assurance.

Researchers at Brigham & Women's Hospital, which reported on this issue in the ***New England Journal of Medicine***, suggested several possible solutions:

- Simply for pharmacists to submit all prescription benefit claims, regardless of method of payment.
- Use the pharmacies' electronic systems for recording transactions and monitoring inventory rather than "prescriptions filled."
- Use electronic health records integrated with pharmacy and insurance claims.

CT scans – new FDA radiation safety recommendations

After investigating reports that at least 385 patients undergoing computed tomography (CT) brain perfusion scans were accidentally exposed to excess radiation, the FDA concluded that, when properly used, the CT scanners themselves did not malfunction. Rather, the FDA blamed the improper use of the scanners on overdoses.

As a result, the FDA is recommending steps to reduce the likelihood of radiation overexposure in the event of improper use of CT. The FDA sent a letter to the Medical Imaging and Technology Alliance, the major professional industry organization for CT manufacturers, with its recommendations, and the Agency plans to hold follow-up discussions with manufacturers.

The recommendations for manufacturers include:

- A console notification to alert the operator of a high radiation dose.
- Clarification of parameters affecting dose, along with clear instructions on how to appropriately set those parameters.
- Providing particular information and training on brain-perfusion protocols to all facilities that receive base CT equipment, whether or not the facilities purchase the related software enabling quantitative analysis of cerebral hemodynamics.
- Organization of all dose-related information into one section of each user manual, in a dedicated dose manual, or indexed comprehensively in a concordance covering all manuals.

Debt reduction proposal – how it would affect healthcare

The bipartisan debt commission appointed by President Obama released its proposed $4 billion, 10-year debt-cutting plan, and while it would eliminate the nation's debt by 2037, one provision would eliminate Medicare's sustainable growth rate (SGR) and replace it with a small reduction in pay to doctors. However, there is disagreement among the 18-member panel, which is due to present the final proposal to Congress on December 1, 2010.

Under the proposed plan, the SGR would be replaced in 2015 with a "modest reduction" for physicians and other providers, but it doesn't say what a "modest reduction" in Medicare reimbursement means. At the same time, the plan calls for the Centers for Medicare and Medicaid Services (CMS) to establish a new payment system that rewards doctors for quality, includes accountable care organizations, and bundles payments by episodes of care.

To pay for SGR reform, the panel will recommend:

- Paying medical malpractice lawyers less, capping non-economic damages in medical malpractice cases, and enacting tort reform.
- Requiring pharmas to pay rebates for brand-name drugs as a condition of participating in Medicare Part D.
- Cutting federal spending on graduate medical education.

Other health-related cost savings measures proposed by the panel include:

- Increasing cost-sharing by military retirees under Tricare and by federal retirees.
- Increasing Medicaid copays.
- Increase cost-sharing in Medicare.

DENDREON's Provenge (sipuleucel-T)

- **CMS to review.** Documents released by CMS in advance of a Medicare Evidence Development and Coverage Advisory Committee (MEDCAC) meeting on November 17, 2010, indicate that an assessment prepared for CMS found the prostate cancer vaccine has "moderate" effectiveness. Historically, Medicare reimburses for on-label uses of FDA-approved drugs, but the panel will discuss whether this high-priced vaccine (~$93,000/year) should be covered.
- **Plant expansion.** Dendreon filed an FDA application to expand its New Jersey plant that manufactures this prostate cancer vaccine from 12 workstations to 36.

Dialysis centers – How clean are they?

An investigative report by ***The Atlantic*** magazine and ***ProPublica*** found that lapses in cleanliness are common at U.S. kidney dialysis centers. After reviewing documents obtained under the Freedom of Information Act and interviewing patients, advocates, doctors, researchers, policy-makers, and industry experts, the reporters found that poor conditions were relatively common. They reported that at nearly half of the facilities, inspectors noted dirty or unsafe conditions, including dried blood in treatment chairs or on walls, floors, and ceilings.

In response, Kidney Care Partners (KCP), a coalition of patient advocates, dialysis professionals, care providers, and manufacturers, said the story "fails to give a full picture of kidney care in America and the progress that has been made." DaVita, a large dialysis provider, called it "irresponsible journalism" and described the end-stage renal disease (ESRD) program as a "role model in our healthcare system and a success story within Medicare." Fresenius, another large dialysis provider, said the story doesn't "fairly or accurately reflect the quality of great care that we provide day in and day out to our patients."

Doctor/pharma relationships – slightly fewer freebies

A survey of 1,891 family physicians, internists, pediatricians, cardiologists, surgeons, psychiatrists, and anesthesiologists found that, compared to a similar survey in 2004, doctors are accepting fewer drug samples, gifts, meals, and all-expenses-paid trips from pharmas.

- In 2009, 84% accepted items vs. 94% in 2004.
- The number of physicians being paid by pharmas for continuing medical education (CME) or attending meetings in expensive or exotic locations dropped nearly in half (to 18% vs. 35%).
- Fewer doctors reported consulting, speaking for companies, or serving on advisory boards.

Dual antiplatelet therapy and PPIs – new guidelines

Experts from the American College of Cardiology, the American College of Gastroenterology, and the American Heart Association have created new consensus guidelines for the use of dual antiplatelet therapy and proton pump inhibitors (PPIs).

Basically, the recommendations, published in the ***Journal of the American College of Cardiology***, say:

- PPIs are recommended for patients with a history of (or multiple risk factors for) upper GI bleeding.
- PPIs are not recommended to reduce prophylactically in patients with a lower risk of upper GI bleeding.
- Future studies are needed of concomitant PPI and anti-platelet use in high-risk cardiac patients with an impaired ability to metabolize antiplatelet drugs (i.e., patients with the CYP2C19 polymorphism). They noted that pharmaco-genomic testing for CYP2C19 variants or platelet function testing could tailor therapy and guide a physician's choice to administer thienopyridines – Sanofi-Aventis's Plavix (clopidogrel) or Lilly's Effient (prasugrel). However, they noted, "Although the concept of individually tailored therapy is rational and attractive, empirical evidence for this approach is sparse."

German drug prices – coming down, forcibly

The lower house of the German parliament approved a bill that would curb pharmas' ability to set prices for prescription drugs. Under the measure, pharmas will have a year to negotiate a price with the German insurers or the German Health Ministry will set a maximum price, and the drugs would undergo a cost:benefit analysis by a semi-state agency. A member of the parliament's Health Committee said, "We are breaking the price monopoly of the pharma industry."

Hypertension – drug use up

Ten-year data (1999 to 2008) from the Centers for Disease Control and Prevention (CDC) show that:

- More people are taking hypertension medications (74% vs. 60%).
- Patient awareness of their high blood pressure increased (from 70% to 81%).
- The prevalence of high blood pressure among U.S. adults (30%) did not change.

- Patients with their blood pressure controlled increased (from 30% to 48%).

Infusion pumps – Will the recalls never end?

The most recent FDA-ordered recall is for WalkMed Infusion's Triton pole mount infusion pump due to a potential door open alarm problem. Users are urged to return the devices to the company, which has begun upgrading all the recalled devices.

JOHNSON & JOHNSON/ETHICON's Sedasys – appeal granted

FDA Commissioner Dr. Margaret Hamburg granted permission for J&J to appeal the Center for Devices and Radiological Health's rejection of this computer-aided sedation device for use in colonoscopy and upper gastrointestinal procedures. The FDA will now appoint a new, independent advisory committee to reconsider the PMA. That panel is likely to recommend approval since the first advisory committee did. *It's not clear how that will help J&J unless it has a new labeling proposal since the FDA's objection was over labeling that would have allowed administration of protocol without an anesthesia professional present, and the FDA has been cracking down on protocol use recently.*

Kidney injury – marker identified

A study published in the ***Journal of the American Society of Nephrology (JASN)*** suggests that a simple urine test could be a red flag for acute kidney injury (AKI) and may help prevent cases of acute kidney failure. The marker is monocyte chemo attractant protein-1, a protein that plays a role in recruiting immune cells to injured or infected sites in the body. It has been found in the joints of rheumatoid arthritis patients and in the urine of lupus patients.

The researchers found that patients with AKI have elevated urine levels of monocyte chemo attractant protein-1 as well as its mRNA. Using a chromatin immunoprecipitation assay, they showed that changes in histones can activate the gene that produces MCP-1. A larger, prospective study is needed to determine the clinical utility of the assay.

MERCK's Gardasil (HPV vaccine) – poor compliance

A University of Maryland single-center study, reported at the American Association for Cancer Research Cancer Prevention meeting, found that fewer than a third of women who get the first human papillomavirus (HPV) vaccine shot complete the three-dose series. In the study of nearly 10,000 eligible females (age 9-26) from 2006 to 2010, electronic health records were used to ascertain that 30.78% of those who started the HPV vaccine regimen actually completed all three doses.

Of the 2,641 women who started the vaccine regimen, 39.1% got 1 dose, 30.1% got 2 doses, and 30.78% completed all 3 doses. Women age ≥18 and African Americans were least likely to complete the regimen.

NIH grants – preparing for cuts

Anticipating that Congress will cut its budget, the National Institutes of Health is looking at ways to cut research grants. NIH Director Dr. Francis Collins told the American Society of Human Genetics meeting, "I don't think it's reasonable to assume that NIH is going to have another doubling [of its budget] anytime soon. One might make the case that it would be better for those funds [used for university faculty salaries to] perhaps be available for other investigators. NIH is supporting an awful lot of salaries, and that seems fair to the degree that they are spending that amount of time on the research. Universities have also discovered that's a great way to build programs but it may be in the long run that this may not be the best way…for research to be supported."

One program likely to get more money from NIH is the new Therapeutics for Rare and Neglected Diseases program, which is working on diseases such as schistosomiasis/hookworm, Niemann-Pick Type C disease, hereditary inclusion body myopathy, sickle cell disease, and chronic lymphocytic leukemia (CLL).

Puerto Rican manufacturing – under Congressional scrutiny

Leaders of the House Committee on Oversight and Government Reform are concerned that the FDA may not have the local staff to properly oversee pharma manufacturing in Puerto Rico. Rep. Edolphus Towns (D-NY) and Rep. Darrell Issa (R-CA) asked the FDA to submit inspection records and warning letters issued during the previous 10 years related to – and FDA actions in conjunction with – problems at GlaxoSmith-Kline's and Johnson & Johnson's Puerto Rican manufacturing plants.

Surescripts Network – to allow exchange of all types of data

Surescripts is opening up its network to support the exchange of all types of clinical information. Through a partnership with Kryptiq, Surescripts will offer tools that can be used with electronic medical record (EMR) systems and e-prescribing systems to enable information to be exchanged among network

participants (EMRs, health information exchanges, health system networks, and pharmacies) even if they aren't on the same network.

VERTEX – HCV trial expansion

Vertex is adding an arm to its ongoing, randomized, parallel-group, dose-ranging Phase II combination trial of telaprevir (a protease inhibitor) + VX-222 (a non-nucleoside polymerase inhibitor) ± pegylated interferon – **Roche**'s Pegasys (pegylated interferon-alfa-2A) in one arm and **Merck**'s PegIntron (pegylated interferon-alfa-2B) in another – in hepatitis C. The new arm will be an oral BID triplet of telaprevir + VX-222 + ribavirin for 12-weeks. The original arms completed enrollment in October 2010, and enrollment in the new arm is scheduled to begin in 1Q11. *Does this reflect experts' doubt that a ribavirin-free oral therapy is feasible today?*

REGULATORY NEWS

FDA reports pharma postmarketing commitments improving

The FDA's annual review of 591 required postmarketing studies for drugs and biologics found that 46% were done, and most of the remaining studies are on track or have been submitted for review. Only 17% were delayed, and 7% that were on schedule after the first review have fallen behind schedule.

FDA cleared, again, of harassing Agency scientists

For the second time this year, the Department of Health and Human Services Office of the Inspector General (OIG) has concluded there is "no evidence" that the FDA retaliated against nine FDA scientists. The scientists had complained they were pressured and harassed by their managers into approving medical devices – CT scanners and radiation-emitting devices – against their judgment. The OIG reached the same finding in February but reopened the investigation at the request of legislators and advocacy groups, who complained that the previous investigation was too narrow and did not look into allegations of misconduct that fell short of criminal violations.

In what was perhaps coincidental timing, the FDA announced that its investigation found that CT scanners are safe when used properly and that overdoses are probably due to operator error.

FDA criticized for hiring "trainers"

Some members of Congress are concerned that the FDA may have wasted millions of dollars on leadership training consultants instead of using the money to catch up on product approvals. The FDA reportedly contracted with **McKinsey & Co.** for $17 million in training since 2008 and with **Leadership Performance Solutions** for $7.9 million.

FDA criticized by GAO for handling of heparin contamination

The Government Accountability Office (GAO) issued a report saying that the FDA's response to the 2008 heparin contamination crisis helped protect the public's health. However, the report also found that the Agency's work with external scientists who had ties to manufacturers of the drug "ran the risk of undermining public confidence in the integrity of FDA's operations." The GAO recommended that FDA "develop adequate controls to help avoid exposure to risks when working with external entities in future situations similar to the heparin crisis."

FDA reclassifies tissue adhesives

The FDA's General and Plastic Surgery Devices Division has classified tissue adhesive with adjunct wound closure devices intended for topical approximation of skin into Class II (special controls). The FDA said it did this to "provide reasonable assurance of safety and effectiveness of the device." This final rule is effective December 10, 2010; the classification was effective April 30, 2010.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	November 2010	
November 16	**GSK/Human Genome Sciences' Benlysta** (belimumab) for lupus	FDA's Arthritis Advisory Committee
November 17	National Coverage Decision meeting on **Dendreon's Provenge** (sipuleucel-T) for prostate cancer	CMS's Medicare Evidence Development and Coverage Advisory Committee (MEDCAC)
November 18	**Amgen's denosumab** for cancer patients	PDUFA date
November 18	**Mela Sciences' MelaFind** for melanoma detection	FDA's General and Plastic Surgery Devices Advisory Committee
November 30	**GlaxoSmithKline/Valeant's ezogabine** for epilepsy	PDUFA date
November 30	Discussion of **pediatric development of four oncology products** that were either recently approved by FDA or, are in late stage development for an adult oncology indication: Pfizer's crizotinib, Allos Therapeutics' Folotyn (pralatrexate), Amgen's denosumab, and Eisai's eribulin	Pediatric Oncology Subcommittee of the FDA's Oncologic Drugs Advisory Committee
	December 2010	
December 1	**GlaxoSmithKline's Avodart** (dutasteride) and **Merck's Proscar** (finasteride) for prostate cancer	FDA's Oncologic Drugs Advisory Committee (ODAC)
December 2	**Bristol-Myers Squibb's Yervoy** (ipilimumab) for advanced melanoma *and* **AstraZeneca/iPR Pharmaceuticals' Zictifa** (vandetanib) for thyroid cancer	FDA's Oncologic Drugs Advisory Committee (ODAC)
December 2	**Oceana Therapeutics' Solesta** (dextranomer in gel of stabilized non-animal hyaluronate) for fecal incontinence	FDA's Gastroenterology and Urology Devices Advisory Committee
December 3	**Allergan's Lap-Band,** expanded indication	FDA's Gastroenterology and Urology Devices Advisory Committee
December 7	**Orexigen Therapeutics' Contrave** (naltrexone + bupropion), a diet drug	FDA's Endocrinologic and Metabolic Drugs Advisory Committee
December 9	**GSK/Human Genome Sciences' Benlysta** (belimumab) for lupus	PDUFA date
December 16	**AstraZeneca's Brilinta** (ticagrelor), an anticoagulant	PDUFA date
December 29	**Mannkind's Afresa** (inhaled insulin)	PDUFA date
	Other future meetings	
January 7, 2011	**Endo Pharmaceuticals' Opana TRF** (oxymorphone ER) for pain	PDUFA date
January 31, 2011	**Orexigen Therapeutics' Contrave** (naltrexone + bupropion), a diet drug	PDUFA date
March 7, 2011	**Salix Pharmaceuticals' Xifaxan** (rifaximin) for non-constipation IBS	PDUFA date
March 26, 2011	**Bristol-Myers Squibb's Yervoy** (ipilimumab) for advanced melanoma	New PDUFA date
Date TBA, 2011	Review of **accelerated drug approval process**	FDA's Oncologic Drug Products Advisory Committee (ODAC)
Summer 2011	Report on **FDA 510(k) reform**	Institute of Medicine