TRENDS-in-MEDICINE

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by Lynne Peterson

Quick Takes

…Highlights from this week's news affecting drugs and devices in development that are not covered in longer *Trends-in-Medicine* reports…

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SHORT TAKES

- **AMGEN AND TAKEDA's motesanib** missed the primary endpoint in a Phase III trial in 1,090 patients with advanced non-squamous non-small cell lung cancer, failing to show a statistically significant improvement for chemotherapy + motesanib vs. chemotherapy alone.
- **AMGEN's Vectibix (panitumumab) –** The company asked the European Medicines Agency (EMA) to reconsider the negative opinion on expanding use for colorectal cancer that was made by the Committee for Medicinal Products for Human Use.
- **APP PHARMACEUTICALS' irinotecan IV –** Five lots of this drug for recurrent/progressive metastatic colorectal cancer were recalled due to foreign material (a fungal microbial contaminant) and non-sterility discovered in one lot. The company said "an atypical trend in customer complaints" alerted it to the problem.
- **DARA BIOSCIENCES' KRN-5500 –** Positive results from a 19-patient, Phase IIa, proof-of-concept trial, which found the drug reduced neuropathic pain associated with cancer vs. placebo, were presented at the 2011 International Conference on Accelerating the Development of Enhanced Pain Treatments.
- **DENDREON's Provenge (sipuleucel-T) –** The Centers for Medicare and Medicaid Services (CMS) proposed paying for this immunotherapy for prostate cancer, despite its $93,000 per patient cost. CMS will accept public comments for 30 days and then issue a final decision 60 days after that.
- **ENTEROMEDICS' Maestro RC System**, an anti-obesity device, received a CE Mark. The implanted pacemaker-like device sends electrical signals through the vagus nerve in the stomach to the brain to suppress hunger. The company said it does not intend to commercialize the device until it gets regulatory approval in Australia, but that is expected in 2H11.
- **GILEAD SCIENCES** signed a multiyear research collaboration with the Yale School of Medicine, focusing on potential cancer treatments. In the first four-year period, Gilead will provide $40 million in research support and basic science infrastructure development and up to $60 million more over the next six years if the collaboration is renewed.
- **Inferior vena cava (IVC) filters –** Preliminary data reported at the Society of Interventional Radiology (SIR) suggested the excimer-laser assisted techniques used to extract cardiac device (e.g., ICD) leads can be used successfully to retrieve the occasional IVC filter that is difficult to remove. Stanford researchers reported on 25 consecutive cases, with a 96% success rate. An ~100-patient pivotal trial is planned to confirm these findings.

- **MAQUET CARDIOVASCULAR's Heartstring II Proximal Seal System**, a device used in CABG to help control the flow of blood in the aorta, was recalled, and the FDA has now upgraded the recall to a Class I recall, because the devices could have insufficient adhesive, causing the deployment tube to detach during use.
- **Medical devices in Japan –** The Japan Federation of Medical Devices Associations (JFMDA) is pushing for regulations that specifically target the medical device industry. The Japanese government plans to revise the country's Pharmaceutical Affairs Law (PAL) next year, and the device industry believes that current regulations stifle innovation and slow approvals because devices and drugs are treated in the same regulatory manner.
- **MERCK KGAA's Erbitux (cetuximab) –** The company refiled its application with the EMA for wider use of this cancer drug.
- **OMEROS' OMS-103HP** missed the primary endpoint in a Phase III trial in patients undergoing arthroscopic reconstructive surgery for an anterior cruciate ligament. The drug was developed to improve joint motion and reduce pain after surgery.
- **Opioid abuse –** The Georgia House of Representatives approved a bill that was already approved by the Georgia Senate (SB 36) that would require pharmacists and doctors who dispense medicines to report to the state weekly on who receives prescriptions for a wide range of potentially addictive drugs. The legislation includes criminal penalties for those who negligently use the new database or release information from it.
- **Parkinson's drugs –** A study published in the journal ***Parkinsonism and Related Disorders*** found that up to 22% of Parkinson's disease patients developed new-onset impulse control (behavioral) problems over two years.
- **PFIZER subsidiary GREENSTONE** recalled one lot of the antidepressant citalopram 10 mg tablets as well as finasteride 5 mg tablets, a drug for benign prostatic hyperplasia (BPH), because of the possibility that a third-party manufacturer mislabeled the citalopram as finasteride.
- **Radiation exposure –** A 54-patient study published in the ***Journal of Vascular Surgery*** found the amount of direct and indirect radiation to which a surgeon is exposed during an endovascular thoracoabdominal aneurysm (eTAAA) repair is equivalent to two preoperative CT scans. Since the maximum surgeon exposure is 50 mSv/year, a surgeon can perform up to 294 eTAAA procedures annually before reaching the maximum allowed radiation dose.
- **SPECTRUM PHARMACEUTICALS' belinostat** will continue a pivotal study in peripheral T-cell lymphoma after the data safety monitoring board said there were no safety issues, despite the failure of a Phase II trial in ovarian cancer.
- **VALEANT PHARMACEUTICALS** is making a hostile bid for **Cephalon**, which first announced it was acquiring **Gemin X Pharmaceuticals** and then announced plans for a take-over bid for **ChemGenex Pharmaceuticals**.
- **VERTEX's VX-770 –** The interim, 24-week results of a 48-week study found VX-770 improved lung function in children (age 6-11) with cystic fibrosis who had a mutation in the G551D gene, with FEV_1 improving 12.5% from baseline. The results are considered exciting even though only ~4% of cystic fibrosis patients have this mutation. These findings confirm similar findings in the Phase III STRIVE trial reported in February 2011.

NEWS IN BRIEF

ACR – issues new guidelines for JIA

The American College of Rheumatology (ACR) issued new guidelines for starting and monitoring treatments of children with juvenile idiopathic arthritis (JIA). The guidelines, which were published in ***Arthritis Care & Research***, cover: NSAIDs, methotrexate, oral and injectable steroids, and biologics. Among the key recommendations:

- Beginning treatment with TNF-α inhibitors in children with a history of:
  - Arthritis in ≤4 joints and significant active arthritis despite treatment with methotrexate.
  - Arthritis in ≥5 joints and any active arthritis following an adequate trial of methotrexate.
- Beginning treatment with Biovitrum's Kineret (anakinra) in children with systemic arthritis and active fever whose treatment requires a second medication in addition to systemic glucocorticoids.

Bariatric surgery and bone loss in adolescents – risk in first two years

A retrospective case review published in the journal ***Pediatrics*** may cause surgeons and parents to think twice about bariatric surgery for children. The study found that obese adolescents lost significant amounts (an average of 7.4%) of bone mineral density (BMD) in the first two years after bariatric surgery. The researchers analyzed the medical records of 61 adolescents who had laparoscopic Roux-en-Y gastric bypass surgery. The BMD loss correlated with the weight loss, but the kids' BMD was still within the appropriate range for their age.

BOEHRINGER INGELHEIM's Pradaxa (dabigatran) – FDA issued *another* handling warning

The FDA issued a special drug safety communication on the storage and handling of Pradaxa. The Agency didn't change the storage/handling advice in the anticoagulant's label, but the FDA is concerned that doctors, pharmacies, and patients are not aware of or following the directions, which can lead to breakdown from moisture and loss of potency.

The FDA noted that many patients use pill boxes or pill organizers to help them remember to take their medications, but Pradaxa should not be stored (or dispensed by pharmacists) in anything but the original package (either a special bottle or blister pack).

Using the original packaging also can extend the life of Pradaxa. The label says the drug should be discarded 30 days after a bottle is opened, but the FDA now says Pradaxa appears to maintain its potency up to 60 days after a bottle is opened – provided it is stored in the original bottle, the cap is closed tightly after each use, and the bottle is kept away from excessive moisture, heat, and cold.

The FDA also wants doctors and pharmacists to emphasize to patients the handling instructions for Pradaxa.

JOHNSON & JOHNSON

- **Invega Sustenna (paliperidone palmitate)** – J&J canceled plans for a head-to-head trial comparing Invega Sustenna with other oral antipsychotics, including its Risperdal (risperidone) and **AstraZeneca**'s Seroquel (quetiapine), but officials did not give a reason.
- **This week's recalls:** (a) One lot (more than 34,000 bottles) of Tylenol extended-release tablets because of the musty/moldy odor that led to earlier over-the-counter drug recalls. The odor is thought to be caused by trace amounts of a chemical used to treat the wooden pallets on which bottles are stored and shipped. (b) J&J also expanded the January 14, 2011, recall of various Tylenol, Benadryl, Sudafed, and Rolaids packages in the U.S., adding 717,000 packages to those already recalled.
- **McNeil reorganization** – As of April 4, 2011, J&J is reorganizing its consumer business, which includes McNeil Consumer Healthcare, into North America, Latin America, Asia-Pacific, and Europe/Middle East/Africa. The move separates the recall-ridden McNeil from other consumer healthcare divisions and, according to J&J, lets the company "give focused attention to quality and compliance, and the critical task of restoring McNeil Consumer Healthcare brands."

Radiation – airport scanners safe

A study published in the ***Archives of Internal Medicine*** found the risk of developing cancer as a result of exposure to ionizing radiation from a full-body scan at the airport is minimal. The researchers estimated that the radiation dose emitted by backscatter X-ray scanners is equivalent to 3-5 minutes of exposure to typical background radiation sources, such as the sun or radon from the earth. They calculated that if 2 million 5-year-old girls flew round trip once a week (and were scanned), there would be only one additional breast cancer over the girls' lifetime. However, the researchers did suggest that independent testing of the scanners should be done.

REGENERON's aflibercept (VEGF Trap) – specialists surveyed on use

A survey by ***Retina Today*** asked retinal specialists how they would use this drug if it were approved by the FDA and if it were paid for by Medicare:

- 49% said use would depend on the price.
- 22% said it would be second-line therapy after either **Roche/Genentech**'s Avastin (bevacizumab) or Lucentis (ranibizumab).
- 17% said Avastin would remain the front-line drug.
- 8% said aflibercept would become their preferred anti-VEGF therapy.
- 4% said they would continue using Lucentis front line.

ROCHE

- **Accu-Chek FlexLink Plus** infusion sets manufactured since November 2010 were recalled because of the possibility of under-delivery of insulin.
- **Dalcetrapib** – The company announced top-line results from two exploratory Phase IIb studies (dal-VESSEL and dal-PLAQUE), both of which showed this first-in-class cholesteryl ester transfer protein (CETP) modulator to raise HDL is safe, with no pro-inflammatory or pro-atherogenic effects, no effect on blood pressure, and good tolerability out to two years. A >17,000-patient dal-HEART trial and the Phase III dal-OUTCOMES trial (which is just that, an outcomes trial) are ongoing, and another Phase III trial, dal-ACUTE, is being initiated.
- **Lucentis (ranibizumab)** – Lucentis met the primary endpoint in a second Phase III trial in diabetic macular edema, RIDE. At 24 months, significantly more Lucentis patients had ≥15 letters in visual improvement (33.6% at 0.3 mg and 45.7% at 0.5 mg vs. 12.3% with sham injection). The full results of the 382-patient, multicenter, randomized, double-

masked, sham-controlled trial will be presented at the EURETINA Congress in London on May 29, 2011.

REGULATORY NEWS

FDA chemist charged with insider trading

The Securities and Exchange Commission (SEC) accused FDA chemist Cheng Yi Liang and his son of insider trading based on non-public information about drugs pending approval by the FDA. The FDA said the two men traded in advance of "dozens" of FDA decisions. Separately, the Justice Department filed criminal charges of wire fraud, securities fraud, and conspiracy.

FDA getting tough with oncology drugmakers

At a meeting of the FDA's Oncology Drugs Advisory Committee (ODAC) in February, Richard Pazdur, MD, director of the FDA's Office of Oncology Drug Products, warned the Agency was likely to start fining pharmas that get accelerated approval for a drug if they don't complete their Phase IV trials in a timely manner. He also said the FDA may require the confirmatory trial to be under way before accelerated approval is granted.

This past week, other FDA officials sounded the same warning in an article in the ***Journal of the National Cancer Institute***. John Johnson, MD, a clinical team leader in the FDA's Division of Drug Oncology Products, and colleagues, citing several postmarketing confirmatory studies that simply have taken too long, wrote, "The FDA believes that this [a fine] will be an effective new tool for dealing with lack of due diligence."

FDA should inspect more overseas suppliers

Two associations representing the fine chemicals industry – the European Fine Chemicals Group (EFCG) and the USA-based Society of Chemical Manufacturers & Affiliates (SOCMA) – are urging the FDA to do more inspections of overseas active pharmaceutical ingredient (API) manufacturers supplying the U.S. market. And the associations are saying fees should be levied on the inspected sites to pay for the inspections.

SOCMA told the FDA that it is inadequately resourced to maintain effective oversight of foreign API facilities, particularly in India and China. The associations also recommended an electronic database be established with information on companies with Drug Master Files (DMFs) filed at FDA, on sites registered with the FDA and the APIs made at those registered sites, and on the outcomes of FDA compliance inspections.

FDA tells pharma to check suppliers' quality efforts

After several drugs had to be recalled because of contamination with glass fragments, the FDA sent a general warning to all pharmas to check the quality management efforts of their suppliers. The FDA wants drugmakers to go over their suppliers' quality-management efforts in light of a number of recalls for glass fragment contamination in drug vials. The Agency advised that the risk of a problem is greater with:

- Vials made with a tubing process that uses high heat.
- Drugs formulated in alkaline solutions and with certain buffers (e.g., citrate and tartrate).
- Products with long shelf life and those stored at room temperature (vs. refrigerated).
- Using lower-grade glass.

Kentucky Medicaid may restrict use of three oncology drugs

Kentucky health officials, trying to contain rising Medicaid costs, are considering restrictions on the use of three unnamed oral drugs without prior approval. The final decision will be made by Cabinet for Health and Family Services Secretary Janie Miller, but the Medicaid Pharmacy and Therapeutics Advisory Committee – which is made up of doctors, pharmacists, and other healthcare providers – voted to follow the recommendations of a private contractor (Magellan) that administers claims for the Medicaid pharmacy program in Kentucky, which was to limit payment for the three oncology drugs. *The question is whether other states will follow suit if Kentucky does restrict use of these drugs.*

Senate Medical Technology Caucus established

In a bipartisan move, Sen. Scott Brown (R-MA) and Sen. Amy Klobuchar (D-MN) organized a new Senate Medical Technology Caucus, which is aimed at tackling legislative issues facing the medical device industry. Sen. Brown said, "It is critical that we provide a business environment for them to innovate, grow, and thrive."

U.K.'s Nice rejects Orencia

Noting that it already approved several biologic therapies for rheumatoid arthritis (RA), the U.K.'s National Institute for Health and Clinical Excellence (NICE) said Bristol-Myers Squibb's Orencia (abatacept) is not cost-effective for National Health Service (NHS) use as second-line treatment for adults with moderate-to-severe RA who are non-responders to non-biologic therapy.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	April 2011	
April 5	**Optimer Pharmaceuticals' fidaxomicin** for the treatment of *C. diff*	FDA Anti-Infective Drugs Advisory Committee
April 7	**AstraZeneca's Zactima** (vandetanib) for inoperable medullary thyroid cancer	PDUFA date
April 7	Online repository of **searchable 510(k) medical device labels and photographs**	FDA's Center for Devices and Radiological Health (CDRH) public meeting
April 10	Open forum to discuss statistical issues related to **drug and biologics development and review**	Joint FDA and Drug Information Agency (DIA) Forum
April 12	**NDA for Novartis's Afinitor** (everolimus) and **sNDA for Pfizer's Sutent** (sunitinib) to treat neuroendocrine tumors	FDA's Oncologic Drugs Advisory Committee
April 13	**KV Pharmaceutical/Hologic's Gestiva** (17-alpha hydroxyprogesterone) to prevent premature birth	PDUFA date
April 14-15	**Cardiovascular Safety and Drug Development:** QT, arrhythmias, thrombosis, and bleeding	Joint FDA/DIA meeting
April 27	**Merck's Victrelis** (boceprevir) for HCV	FDA's Antiviral Advisory Committee
April 27	**Medicis Aesthetics' Restylane** – expanded indication for augmentation of the lips	FDA's General and Plastic Surgery Devices Advisory Committee
April 28	**Vertex Pharmaceuticals' telaprevir** for HCV	FDA's Antiviral Advisory Committee
	Other future 2011 meetings/events	
May 4-5	**Biosimilar challenges and opportunities**	Joint DIA and FDLI conference
May 12	**BioMimetic Therapeutics' Augment Bone Graft**, an alternative to autologous bone grafts (PMA application)	FDA's Orthopaedic and Rehabilitation Devices Advisory Committee
May 23	**Vertex Pharmaceuticals' telaprevir**, a treatment for hepatitis C	PDUFA date
May 29	**Roche/Genentech's Lucentis** (ranibizumab) – results of Phase III trial	EURETINA Congress in London
May 30	**Optimer Pharmaceuticals' fidaxomicin** for the treatment of *C. diff*	PDUFA date
June 17	**Celgene's Istodax** (romidepsin) – sDNA for peripheral T-cell lymphoma	PDUFA date
June 17	**Pfizer/King Pharmaceuticals' Acurox** (immediate-release oxycodone), a painkiller	PDUFA date
June 23	**Pfizer/King Pharmaceuticals/Pain Therapeutics' Remoxy** (tamper-resistant oxycodone CR) for pain	PDUFA date
June 28-29	**Roche/Genentech's Avastin** (bevacizumab), hearing on appeal of FDA's decision to withdraw the indication for metastatic breast cancer	FDA's Oncologic Drugs Advisory Committee (ODAC)
July	**Novartis's Arcapta Neohaler** (indacaterol) long-acting beta agonist (LABA) for COPD	PDUFA date
July 20	**AstraZeneca's Brilinta** (ticagrelor), an anticoagulant	PDUFA date
August 25	**Shire's Firazyr** (icatibant) for hereditary angioedema	PDUFA date
2H11	**Abbott's RX Acculink** carotid stent	FDA final decision expected
Summer	Report on **FDA 510(k) reform**	Institute of Medicine
4Q11	**Ophthotech's ARC-1905** primary endpoint results in Phase I trial in dry AMD	Company announcement or medical conference presentation
4Q11	**Roche/Genentech's Lucentis** (ranibizumab) – Phase III HARBOR trial one-year data on the 2 mg dose in wet AMD	Company announcement or medical conference presentation
October 20	**Johnson & Johnson's abiraterone** for metastatic prostate cancer	PDUFA date
December	**Allergan's brimonidine tartrate intravitreal implant** – Phase II trial in dry AMD to complete	Company announcement or medical conference presentation
	2012 meetings/events	
February 2012	**Alcon's tandospirone** for dry AMD – Phase III final data expected	Company announcement or medical conference presentation