TRENDS-in-MEDICINE

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by Lynne Peterson

Quick Takes

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

Trends-in-Medicine
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SHORT TAKES

- **ALIMERA SCIENCES and PSIVIDA's Iluvien (sustained-release fluocinolone acetonide)** showed statistically significant results in two Phase III trials in diabetic macular edema. The FDA rejected Iluvien in 2010, asking for additional safety and efficacy data. The companies hope these new data will answer the FDA's questions.
- **ALLERGAN and MAP PHARMACEUTICALS** plan to co-promote Map's Levadex (oral, inhaled dihydroergotamine) for acute migraine in the U.S. to neurologists and pain specialists. Map retains U.S. primary care rights and OUS rights. Map is expected to file the NDA in 1H11.
- **ARENA PHARMACEUTICALS Lorqess (lorcaserin)** – The FDA wants several additional studies on this diet drug, including a 12-month study in female rats to see if a temporary increase in prolactin levels correlates with mammary tumors. The question is whether this will push the resubmission into 2012.
- **ASTRAZENECA's Brilinta (ticagrelor)** – The new FDA decision date for this anticoagulant is July 20, 2011.
- **B. BRAUN's 400ES Safety Infusion System** – The FDA issued a Class I recall, saying the IV infusion systems can develop a memory leak, causing the hardware to become unresponsive and stop operating. Customers are advised to deactivate the wireless communication on their pumps and return them to the manufacturer.
- **BAYER's regorafenib (BAY-73-4506)** was granted orphan drug status by the FDA for the treatment of gastrointestinal stromal tumors (GIST). A pivotal, double-blind, 170-patient, placebo-controlled Phase III study began in January 2011 in patients refractory to Pfizer's Sutent (sunitinib) and Novartis's Gleevec (imatinib). The primary endpoint is progression-free survival (PFS), and secondary endpoints include overall survival (OS), time to progression (TTP), disease control rate (DCR), tumor response rate (RR), duration of response (DOR), and safety.
- **Flu vaccines** – On February 25, 2011, the FDA's Vaccines and Related Biological Products Advisory Committee will discuss and make recommendations on the selection of strains to be included in the influenza virus vaccine for the 2011-2012 influenza season. The committee also will hear an update on Pandemic Influenza Surveillance.
- **Healthcare reform law** – A Federal judge in Florida ruled that President Obama's healthcare reform law – the Affordable Care Act (ACA) – is unconstitutional, siding with 26 states that had sued to overturn the law because of the requirement for people

to buy health insurance. The Department of Justice plans to appeal, and the law remains in effect, but it undoubtedly will eventually have to be resolved by the Supreme Court.

- **ICAGEN's ICA-105665** – The FDA lifted the clinical hold on this epilepsy drug that was imposed in September 2010 after a patient had a serious adverse event in a photosensitivity trial, allowing the company to resume testing.

- **JOHNSON & JOHNSON/CORDIS** – A Texas jury ordered the company to pay $482 million to Dr. Bruce Saffran, determining that the Cypher stent infringed one of the doctor's patents. If the judge doesn't overturn the verdict, J&J plans to appeal.

- **LILLY and BRISTOL-MYERS SQUIBB's necitumumab** – Enrollment was stopped in a study in combination with Lilly's Alimta (pemetrexed) + cisplatin as first-line therapy in advanced non-small cell lung cancer. The independent data monitoring committee had recommended no new or recently enrolled patients continue treatment because of safety concerns. However, Lilly reportedly is continuing another Phase III trial of necitumumab + its Gemzar (gemcitabine) + cisplatin.

- **MYRIAD GENETICS** believes it has a test that might rescue **Sanofi-Aventis's iniparib** (BSI-201), a PARP inhibitor which missed both co-primary endpoints in a pivotal Phase III breast cancer trial. Myriad's test identifies patients with mutations in the BRCA1 and BRCA2 genes. So, if Sanofi's detailed analysis of the Phase III results finds that the drug works in women with a particular BRCA status, the Myriad test might be able to pre-select patients for another trial.

- **NPS PHARMACEUTICALS' Gattex (teduglutide)** – An 86-patient Phase III trial found this adult short bowel syndrome treatment reduced patient dependency on IV fluids more than placebo (63% vs. 30% or 4.4 fewer liters vs. 2.3 fewer liters). NPS plans to submit Gattex to the FDA in 2H11, but **Nycomed**, which has the OUS rights, plans to file the drug with European regulators in 1H11.

- **ONYX PHARMACEUTICALS' carfilzomib** was granted fast track status by the FDA. It already had orphan drug status. The company plans to complete its FDA submissions by mid-year.

- **Patent law** – Sen. Patrick Leahy (D-VT) and Sen. Charles Grassley (R-IA) introduced a bill that would change the U.S. patent system from a first-to-invent to a first-to-file system.

- **PFIZER** is cutting its spending on R&D by up to $2.9 billion over the next two years, closing its facility in Sandwich, U.K., and reducing the Groton CT workforce by 1,100 people, though it will add jobs in Boston and in Cambridge, U.K. The company reportedly will stop research funding for allergy, urology, respiratory, internal medicine, and tissue repair, focusing instead on cancer, neuroscience, inflammation, vaccines, and immunology.

- **ROCHE's taspoglutide** – After an extensive analysis of the Phase III data, Roche is abandoning this Type 2 diabetes drug and returning it to **Ipsen**. Dosing in the trials was stopped in September 2010 because of an excessively high dropout rate, due primarily to nausea and vomiting, and because of hypersensitivity reactions. Roche had been trying to figure out what caused the side effects and how to reformulate the medication, but it is now giving up on it instead.

- **SANOFI-AVENTIS's lixisenatide**, a once-daily drug for Type 2 diabetes, met the primary endpoint in a Phase III trial, with patients experiencing fewer goal hypoglycemic events vs. Lilly/Amylin's Byetta (exenatide).

- **SORIN's Perceval**, a self-anchoring percutaneous aortic valve, received a CE Mark.

- **TEVA** received a warning letter from the FDA about its oral solid dosage plant in Jerusalem, Israel.

- **VALEANT PHARMACEUTICALS/BIOVAIL** is buying the U.S. and Canadian rights for non-eye care uses to **GlaxoSmith-Kline's Zovirax** (acyclovir).

NEWS IN BRIEF

Bisphosphonates – may prolong life

A 362-patient study published in the ***Journal of Clinical Endocrinology & Metabolism*** found that patients taking a bisphosphonate for osteoporosis got a survival benefit; they lived five years longer than patients who took another treatment (e.g., calcium, vitamin D, or hormone therapy) or who took nothing. The mortality rate for women on bisphosphonates was 0.8% per 100 person-years vs. 1.2% for women taking hormone therapy, 3.2% for women taking calcium and vitamin D, and 3.5% for women taking no treatment. There was also a survival benefit for men.

CORTEX PHARMACEUTICALS' CX-1739 – positive early results in sleep apnea

The results of a one-night, single-dose, 20-patient sleep lab study found that this drug, intended to treat moderate-to-severe sleep apnea, were sufficient to warrant taking the drug into a larger study. CX-1739 appeared safe, but the dose appeared to be near the limits of tolerability when administered just before bedtime to this moderately

overweight (mean BMI >31), middle-aged (~50-year-old) group of sleep apnea patients. There were no serious adverse events, and no clinically relevant changes in vital signs, cardiovascular or other safety assessments. Adverse events were generally mild-to-moderate, with no new unexpected adverse events.

Results of CX-1739 in Sleep Apnea

Measurement	CX-1739 vs. placebo	p-value
Mean apnea/hypopnea index (AHI or frequency of apnea or hypopnea events per hour of sleep)	Not reduced	---
>40% reduction in AHI	20% vs. 0	---
Change in AHT (apnea/hypopnea time)	Down 21 mins vs. up 12 mins	<0.05
>40% reduction in AHT	30% vs. 0	---
Increase in mean blood oxygen saturation	N/A	<0.01
Increase in minimum blood oxygen saturation	N/A	<0.001
Time blood oxygen saturation <90%	N/A	<0.05

GLAXOSMITHKLINE's Pandemrix, an H1N1 flu vaccine – WHO launches safety review

The World Health Organization (WHO) launched a safety review of Pandemrix in light of a Finnish study indicating that the H1N1 flu vaccine contributed to narcolepsy in people ages 4 to 19 in 2009 and 2010. Last year, the European Medicines Agency said it found no evidence that validates the link.

A preliminary Finnish study by the National Narcolepsy Task Force found an increased incidence of narcolepsy among children in Finland who were inoculated with Pandemrix vs. children who did not get the vaccine. Of the 60 children/adolescents in Finland who contracted narcolepsy in 2009 and 2010, 87% had received Pandemrix. The U.K.'s Medicines and Healthcare products Regulatory Agency (MHRA) cautioned that there is no confirmed link between the vaccine and narcolepsy, pointing out that no signal has been seen outside of Scandinavia and calling for additional studies.

OPTIMER PHARMACEUTICALS' fidaxomicin – study showed effectiveness

A randomized, double-blind, 629-patient Phase III non-inferiority study published in the ***New England Journal of Medicine*** found that a 10-day course of this BID macrocyclic antibiotic is as effective as vancomycin in treating *Clostridium difficile* (*C. diff*) diarrhea, with lower rates of recurrence within four weeks of stopping treatment (15.4% vs. 25.3%, p=0.005). The cure rate for both drugs was similar: 88.2% fidaxomicin vs. 85.5% vancomycin. There was no significant difference in the time to resolution of diarrhea between the two drugs.

OREXIGEN AND TAKEDA's Contrave (naltrexone + bupropion) – another diet drug fails

The FDA rejected Contrave, saying in a complete response letter that a long and large, randomized, double-blind, placebo-controlled study would be required before approval to rule out the risk of major adverse cardiovascular events.

Prions – a blood test in development

Researchers in the U.K. have developed a blood test, using an antibody from D-Gen, that can detect the abnormal prion proteins responsible for variant Creutzfeldt-Jakob disease (vCJD), known as mad cow disease. The results of the study, which compared 21 patients with vCJD to 169 normals, were published in ***The Lancet***. The test correctly identified the abnormal proteins in 15 of the 19 vCJD patients, with no false positives.

The assay was validated by testing 21 vCJD patients, 27 patients with another form of CJD, 42 patients with other neurological diseases, and 100 healthy volunteers. The sensitivity was 71.4% and the specificity 100% (with a confidence interval of 97.8% to 100%).

However, the researcher warned that the sensitivity must be improved and the specificity confirmed in much larger studies before the test could be used to screen asymptomatic people. A minimum specificity of 99.85% is needed for the test to be clinically acceptable.

In an accompanying editorial, an FDA researcher warned that the levels of abnormal prion proteins may be lower in asymptomatic patients, so both specificity and sensitivity need to be confirmed.

Rheumatoid arthritis – new definition of remission

The American College of Rheumatology (ACR) released two new provisional definitions of rheumatoid arthritis (RA) remission, and the new definitions are to be applied to future RA trials. The definitions will be published in the March issue of ***Arthritis & Rheumatism***. A person with RA enrolled in a clinical trial will need to meet one of the following definitions to be considered in remission:

1. Tender joint count, swollen joint count (on 28 joint counts), C-reactive protein (CRP), and patient global assessment (PGA) scores (on a scale of zero to 10) all ≤1.
2. Simplified Disease Activity Index (tender joint count, swollen joint count, CRP, and PGA together + physician global assessment) score ≤3.3.

The ACR said the new definitions "are in line with the RA treatment goal of reversing disease activity to prevent future damage." Basically, the new definition means that a person with essentially no signs and symptoms of the disease would be considered in remission.

ROCHE/GENENTECH's Avastin (bevacizumab) – more bad news

A meta-analysis of 16 studies with 10,217 patients, published in the ***Journal of the American Medical Association***, found that cancer patients treated with Avastin + chemotherapy had nearly 50% more fatal adverse events vs. control patients getting chemotherapy without Avastin (2.5% vs. 1.7%, or 148 events vs. 72 events, p=0.01). The most common fatal adverse event was hemorrhage. The mortality association depends on the Avastin dose and the type of chemotherapy combined with Avastin, with taxanes and platinum drugs having the highest risk.

However, the researchers pointed out that the overall risk of a fatal adverse event was low, so the risk should be weighed against the benefits.

Technetium-99m (Tc-99m) shortage – alternative approved

The FDA approved an alternative to Tc-99m for SPECT imaging, particularly bone scans, a new formulaton of sodium fluoride F18. There has been a nationwide shortage of Tc-99m for more than a year. Sodium fluoride F18 was first approved in 1972 but withdrawn in 1975 when Tc-99m, a cheaper alternative, became available.

The new formulation of sodium fluoride F18, which can be used with PET instead of SPECT imaging, is still more expensive than Tc-99m, but it doesn't have supply problems, and it can be produced by many academic universities and commercial suppliers in the U.S. Interestingly, this new strength sodium fluoride F18 was not submitted to the FDA by industry but by the National Cancer Institute (NCI), which hopes that multiple companies and institutions will submit ANDAs to the FDA so that generic versions of the drug can be produced, allowing for cheaper supplies.

On March 2, 2011, the FDA is holding a public meeting on how to prepare NDAs or ANDAs for sodium fluoride F18 as a PET imaging agent – along with NDAs and ANDAs for fludeoxyglucose (FDG) 18 injection and ammonia N13 injection. By December 12, 2011, the FDA expects all producers of PET drugs in commercial clinical use to begin submitting applications for marketing approval.

REGULATORY NEWS

CMS chose companies for an imaging demonstration

The Centers for Medicare & Medicaid Services (CMS) selected five participants for the two-year Medicare Imaging Demonstration, a project to promote appropriate utilization of advanced imaging services. The project will assess the impact of decision support systems used by physician practices on the appropriateness and utilization of advanced medical imaging services ordered for beneficiaries in original fee-for-service Medicare. The focus of the demonstration is on MRI, CT, and nuclear medicine, and it includes 12 advanced imaging procedures: SPECT, myocardial perfusion imaging, MRI (brain, lumbar spine, knee, and shoulder), and CT (lumbar spine, brain, sinus, abdomen, pelvis, and thorax).

FDA budget facing possible cut

Republican effort to control the federal budget may fall hardest on the FDA, the IRS, the Departments of Commerce, Agriculture, and Housing and Urban Development. Also at risk is health research funding. But experts say Medicare and Medicaid budgets may be safe.

FDA reaching out for help on liver toxicity studies

The FDA is collaborating with Optivia Biotechnology to study how dietary supplements – e.g., black cohosh, green tea, gingko biloba, kava, usnic acid, etc. – interact with acetaminophen and other medicines linked to liver toxicity. The collaboration will initially focus on seven drug transporters that the Agency and the International Transporter Consortium consider most clinically relevant to adverse interactions.

Healthcare IT national coordinator stepping down

Dr. David Blumenthal, National Coordinator for Health Information Technology in the Department of Health and Human Services (HHS), said he will leave this spring after just two years in the job. Among the challenges facing his successor is a Republican proposal to repeal the incentive program for meaningful use of electronic health records (EHRs).

MIM Software's Mobile MIM application cleared

The application has received 510(k) clearance from the FDA, making it the first mobile image viewing application for diagnostic use on Apple iPhones and iPads.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	February 2011	
February 8	Review of **postmarketing studies for cancer drugs** receiving accelerated approval prior to January 1, 2009	FDA's Oncologic Drugs Advisory Committee (ODAC)
February 9	Public workshop on expanding ***in vivo* biomarker detection devices**, focusing on research opportunities and technical challenges	FDA and the Defense Advanced Research Projects Agency (DARPA)
February 12	Presentation of full details of Phase III trial of **Regeneron Pharmaceuticals/Bayer's afilbercept** (VEGF Trap-Eye)	Angiogenesis, Exudation, and Degeneration 2011 conference at Bascom Palmer Eye Institute in Miami
February 25	Discuss and make recommendations on the selection of **strains to be included in the influenza virus vaccine** for the 2011-2012 influenza season and hear an update on Pandemic Influenza Surveillance	FDA's Vaccines and Related Biological Products Advisory Committee
	March 2011	
March 2	Discussion of **innovative approaches to the development of drugs for orphan and rare disease**, including how to utilize biomarkers and pharmacogenetics	FDA Pharmaceutical Sciences and Clinical Pharmacology Advisory Committee meeting in Dallas, Texas
March 2	Session on how to prepare NDAs/ANDAs for **sodium fluoride F18** as a PET imaging agent	FDA public meeting
March 5 (approx.)	**Merck KGaA's cladribine** for multiple sclerosis	PDUFA date
March 7	**Salix Pharmaceuticals' Xifaxan** (rifaximin) for non-constipation IBS	PDUFA date
March 8	**Novartis's Arcapta Neohaler** (indacaterol maleate), a QD bronchodilator for long-term use in COPD	FDA's Pulmonary-Allergy Drugs Advisory Committee
March 10	Risk of **neurodegeneration in pediatric patients** from anesthetic drugs	FDA's Anesthetic and Life Support Drugs Advisory Committee
March 10	**GlaxoSmithKline's Lamictal XR** (lamotrigine extended-release) and discussion of use of historical-controlled trials as a comparator for anticonvulsant monotherapy in epileptic seizures	FDA's Peripheral and Central Nervous System Drugs Advisory Committee
March 10	**Human Genome Sciences/GSK's Benlysta** (belimumab) for lupus	PDUFA date
March 16	Preliminary decision on **how to cover ESAs** for kidney disease patients	CMS decision
March 26	**Bristol-Myers Squibb's Yervoy** (ipilimumab) for advanced melanoma	PDUFA date
	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 7-8	**FDA 510(k) reform**	FDA public meeting
April 10	Open forum to discuss statistical issues related to **drug and biologics development and review**	Joint FDA and Drug Information Agency Forum
April 13	**KV Pharmaceutical/Hologic's Gestiva** (17-alpha hydroxyprogesterone) to prevent premature birth	PDUFA date
	Other future 2011 meetings/events	
May 23	**Vertex Pharmaceuticals' telaprevir**, a treatment for hepatitis C	PDUFA date
May 30	**Optimer Pharmaceuticals' fidaxomicin** for the treatment of *C. diff*	PDUFA date
June 16	Final decision on **coverage of ESAs** for kidney disease patients	CMS decision
June 23	**Pfizer/King Pharmaceuticals/Pain Therapeutics' Remoxy** (tamper-resistant oxycodone CR) for pain	PDUFA date
July 20	**AstraZeneca's Brilinta** (ticagrelor), an anticoagulant	***New*** PDUFA date
Summer	Report on **FDA 510(k) reform**	Institute of Medicine
2H11	**Abbott's RX Acculink** carotid stent	FDA final decision expected
October 20	**Johnson & Johnson's abiraterone** for metastatic prostate cancer	PDUFA date