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

- **Antipsychotics** – The FDA announced new warning labels for all antipsychotics – older agents as well as new atypicals – about the risks in pregnancy, including extra-pyramidal symptoms (EPS) and withdrawal symptoms in newborns whose mothers were treated with them during the third trimester. The FDA said it had reports of 69 episodes of neonatal EPS or withdrawal through October 2008, with symptoms including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder.

- **BIOGEN IDEC/ELAN's Tysabri (natalizumab)** – Cases of progressive multifocal leukoencephalopathy (PML) now total 95 since the multiple sclerosis drug was reintroduced in 2007, and there are now a total of 20 fatalities (including 4 new deaths) this year.

- **Biosimilars** – Speaking to the Generic Pharmaceuticals Association meeting, FDA Commissioner Dr. Margaret Hamburg said her agency plans to release "very soon" regulations to create a pathway for approving follow-on biologics. *The question is what studies the FDA will require, but Dr. Hamburg didn't provide any clarity on that.*

- **CIGNET HEALTHCARE** was fined $4.3 million by the Department of Health and Human Services (HHS) for HIPAA violations.

- **FOREST LABORATORIES** is acquiring **Clinical Data**, which received FDA approval in January 2011 for its antidepressant Viibryd (vilazodone), a selective serotonin reuptake inhibitor and a 5-HT1A receptor partial agonist for the treatment of major depressive disorder (MDD). Forest plans to launch Viibryd in the U.S. in 2H11.

- **GILEAD SCIENCES** is acquiring privately held **Calistoga Pharmaceuticals**, a biotechnology company that develops cancer and inflammatory disease medications.

- **HUMAN GENOME SCIENCES** alleged in a lawsuit that **Roche/Genentech** colluded with **Celltech R&D** (now part of **UCB Pharma**) to fraudulently extend the life of the disputed Cabilly patent, which protects technology using recombinant DNA. Human Genome Sciences wants damages and an injunction preventing Genentech from enforcing its patent on the drug.

- **LILLY/AVID PHARMACEUTICALS' Amyvid (florbetapir)** – In January 2011, the FDA's Peripheral and Central Nervous System Drugs Advisory Committee voted 16-0 that this injectable positron emission tomography (PET) brain imaging agent designed to screen for Alzheimer's disease should be approved, but with a validated training program. However, Public Citizen's Health Research Group doesn't agree. Dr. Sidney

Wolfe wrote to Dr. Janet Woodcock, director of the FDA's Center for Drug Evaluation and Research, that the data are insufficient, not repeatable, inconsistent, and not representative of the population in which it would be used.

- **Malaria** – Researchers at the Georgia Institute of Technology discovered a class of seaweed defense compounds, known as bromophycolides, that may be the source of a new treatment for malaria. The next step would be preclinical animal studies.

- **Meningitis** – The University of Nevada, Reno, and **Immuno-Mycologics** are collaborating to create a new, low-cost, rapid, point-of-care blood test for the early diagnosis of cryptococcal (fungal) meningitis, a leading cause of AIDS-related deaths in developing countries.

- **NICOX's naproxcinod** – The company said it plans to appeal the FDA's rejection of this anti-inflammatory drug. *Hmm, after **Roche/Genentech**'s appeal on Avastin for breast cancer, are appeals going to become more common?*

- **NOVARTIS/CHIRON's tifacogin** – A randomized, 2,138-patient, multinational study, CAPTIVATE, which was published in the American Thoracic Society's ***American Journal of Respiratory and Critical Care Medicine***, found that use of this intravenous anti-clotting drug, a recombinant tissue factor pathway inhibitor, does *not* improve outcomes vs. placebo in patients with severe community-acquired pneumonia (sCAP). Tifacogin had shown some potential benefit in the sCAP subgroup in an earlier study of sepsis patients. *This doesn't come as much of a surprise since other trials have failed as well.*

- **PET changes** – The U.S. Pharmacopeial Convention is proposing changes in the rules for compounding of radiopharmaceuticals for PET scans. The changes include the addition of microbiological testing of locations where PET drugs are prepared, more quality control measures for PET drug development, and a requirement for proper training of PET drug developers. Public comments on the proposals can be made until March 31, 2011.

- **PFIZER/KING PHARMACEUTICALS' Acurox (oxycodone immediate-release)** – The FDA granted priority eview designation for this painkiller, and the new PDUFA date is June 17, 2011. Presumably, this is the new non-niacin-containing version.

- **ROCHE/GENENTECH's Avastin (bevacizumab)** – The FDA has scheduled a two-day meeting (June 28-29, 2011) of its Oncologic Drugs Advisory Committee (ODAC) on the company's appeal of the FDA's decision to withdraw the indication for treating metastatic breast cancer that was granted under accelerated approval but failed to show a benefit in the postmarketing trial.

  Don't think this meeting indicates any softening of the FDA position; it's pro forma to hold the panel. However, the politics of the decision over Avastin in breast cancer have escalated since the final decision will be made by Dr. Hamburg.

- **SALIX PHARMACEUTICALS' Xifaxin (rifaximin)** – The company said the FDA advised them that it planned to issue a complete response letter for Xifaxin in non-constipation irritable bowel syndrome (IBS) and IBS-related bloating. The FDA apparently wants additional information on retreatment, including a longer-term clinical trial in patients experiencing recurrent symptoms.

- **SAMSUNG GROUP** is getting into the pharma business, partnering with **Quintiles Transnational** to make biologic drugs. Samsung Group plans to expand into producing copies of biologics, such as **Roche/Biogen Idec**'s Rituxan (rituximab), for overseas markets.

- **SANTARUS's Rhucin** – The company's Dutch partner, **Pharming**, initiated a 50-patient, 12- to 18-month, Phase III trial of this experimental treatment for hereditary angioedema. Santarus could use the results as supportive data if the FDA asks for more data.

- **UPSHER-SMITH LABORATORIES** – First there was a recall of the company's generic warfarin tablets, and now that recall has been expanded to include six other drug product lines that use the same packaging line.

- **US WORLDMEDS** received a grant of ~$3 million from the National Institute on Drug Abuse to develop non-narcotic treatments for substance-abuse disorders. The company plans to use the money to test its lofexidine, a non-narcotic treatment to treat the symptoms of heroin and opiate withdrawal.

NEWS IN BRIEF

Bariatric surgery – what works best for Type 2 diabetes?

Two studies published in ***Archives of Surgery*** suggested that bypass surgery is better than other bariatric procedures for resolving Type 2 diabetes.

- A one-year, pair-matched, cohort analysis of 185 patients by researchers at the University of California San Francisco found that Roux-en-Y gastric bypass surgery was significantly more effective than **Allergan**'s Lap-Band in improving or resolving Type 2 diabetes (76% vs. 50%, p=0.04). The bypass patients lost significantly more weight

than the Lap-Band patients (64% of excess weight vs. 36%, p<0.01). Quality of life also was better with bypass surgery.

- A randomized trial conducted in Taiwan also found that gastric bypass (but not Roux-en-Y) was more effective than sleeve gastrectomy in resolving Type 2 diabetes (93% vs. 47%, p=0.02). This trial was unusual because it allowed normal-weight people to enter the study.

Heparin – congressional investigation into contamination

The House Energy and Commerce Committee reopened its investigation into the 2008 Chinese heparin contaminated with oversulfated chondroitin sulfate (OSCS). Chairman Fred Upton (R-MI) and Rep. Michael Burgess (R-TX) – who want to know how the adulteration happened "so that industry and government can take more effective proactive measures to reduce the risk of such adulteration in the future" – asked the FDA to release all documents related to the FDA's investigation of the problem within two weeks.

In their letter to FDA Commissioner Dr. Hamburg, the congressmen said, "There is reason to believe all or some of the individuals responsible for the adulteration are still actively engaged in the Chinese pharmaceutical supply chain and pose a continuing threat to pharmaceutical products imported to the U.S." They said that, despite repeated inquiries over the past three years, federal officials have "largely ignored" their questions about the incident.

Hepatitis C virus (HCV) – lack of insurance limits outlook for new therapies

A study published in ***Hepatology***, the journal of the American Association for the Study of Liver Diseases (AASLD), found that U.S. patients with HCV are twice as likely to be uninsured than people without the disease. The researchers, using the NHANES database from 2005-2008, estimated that only one-third of people with HCV have access to antiviral therapy, either because of lack of insurance or contraindications for therapy. The study found:

- 1.16% of individuals studied were HCV-positive.
- 61% of these had medical insurance.
- 67% of HCV-positive patients were eligible for treatment, but only 54% of those had insurance.
- 36% of HCV-positive patients eligible for antiviral therapy had health insurance.

JOHNSON & JOHNSON – more recalls

- **Simponi (golimumab)** – The company withdrew two lots of injection devices preloaded with Simponi from the U.S. and Europe due to a manufacturing problem discovered during routine quality testing that might prevent full-dose delivery of this therapy for rheumatoid arthritis. J&J said this will cause shortages in Europe. Production of new pens will start by the end of this month; the European shortages may last until May.
- **Sudafed (phenylephrine)** – The company pulled nine lots of extended-release Sudafed in the U.S. because of a "typographical error" in the directions on the label. *Will the recalls ever stop?*

Myeloproliferative neoplasms (MPNs) – potential new treatment discovered

Researchers at the University of Florida, working with colleagues in the U.K. and Hungary, discovered a drug they are calling G6 that targets MPNs, a group of life-threatening and hard-to-diagnose diseases that occur when the bone marrow cranks out too many red blood cells, white cells, or platelets because of a mutant form of JAK2. G6 is a stilbenoid, a family of substances known to slow cell growth and which have antioxidant and tumor-suppressing properties.

In cell cultures and mouse studies, G6 reduced swelling in the spleen, corrected the unhealthily low ratio of white to red blood cells in the bone marrow, and decreased the percentage of immature blood cells circulating through the body.

The potential advantage of this agent over the JAK inhibitors already in development is that G6 appears to change the blood cell composition within the bone marrow, which JAK inhibitors do not do.

The discovery is detailed in an article in the ***Journal of Biological Chemistry***. Human clinical trials are expected to start in about a year. So far, the research has been funded in part by the National Institutes of Health (NIH) and the American Heart Association, but the researchers need additional funding to get G6 into the clinic.

PROTALIX BIOTHERAPEUTICS' taliglucerase alfa – rejected by FDA

The company received a complete response letter from the FDA for this synthetic form of glucocerebrosidase to treat Gaucher disease. The Agency said it was dissatisfied with several elements of the company's new drug application (NDA), mostly relating to clinical and chemistry,

manufacturing, and controls (CMC) – testing specifications and assay validation, in particular. The FDA asked for additional data from two trials that were completed after the drug was submitted to the FDA.

Genzyme's Cerezyme (imiglucerase alfa) has been in short supply since 2009 due to manufacturing problems at a Genzyme plant, causing rationing. The FDA temporarily allowed Protalix to distribute taliglucerase alfa during the Cerezyme shortage, but that shortage was recently resolved.

SANOFI-AVENTIS – in trouble with the FDA

Sanofi was warned by the FDA that it has not been reporting potential adverse drug effects or the results of postmarketing studies in a timely manner. And:

- The FDA is not satisfied with the corrective actions the company promised when these deficiencies were brought to its attention three times last year (June, July, and October 2010).
- The FDA said the company doesn't have appropriate procedures for preventing contamination and for staff training at one of its German plants.
- The FDA said Sanofi did not include postmarketing trial information on its diabetes drug Apidra (insulin glulisine), colon cancer drug Eloxatin (oxaliplatin), antibiotic Ketek (telithromycin), and insomnia drug Ambien (zolpidem) in its annual report to the Agency.

Sanofi insisted the issues "will not disrupt its ability to supply products." *But that is exactly what could happen unless Sanofi acts quickly and decisively now.*

Vertex's VX-770 – remarkable results in cystic fibrosis

The results of the Phase III STRIVE trial showed that this oral drug had very good efficacy in a small subset of cystic fibrosis (CF) patients, those with a mutation in the G551D gene. The trial met the primary endpoint and all the key secondary endpoints. And the results at Week 24 were sustained out to Week 48:

- FEV_1 improved 10.6% vs. placebo ($p<0.0001$) at Week 24 (the primary endpoint) and 10.5% at Week 48 ($p<0.0001$).
- VX-770 patients had 55% fewer pulmonary exacerbations and gained an average of 3.1 kilograms at Week 48.
- Sweat chloride was significantly reduced in VX-770 patients vs. placebo.
- VX-770 patients reported fewer respiratory symptoms vs. placebo.
- There was more headache, upper respiratory tract infections, nasal congestion, rash, dizziness, and bacteria in the sputum.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
March 2011		
March 2	Discussion of **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' Arcapta Neohaler** (indacaterol maleate), a QD bronchodilator for long-term use in COPD	FDA's Pulmonary-Allergy Drugs Advisory Committee
March 8-9	Recommendation on scientific issues concerning direct-to-consumer (DTC) genetic tests that make medical claims	FDA's Molecular and Clinical Genetics Advisory Committee
March 10	**Roche/Genentech's Lucentis** (ranibizumab) Phase III RISE results in DME	The Macula Society meeting
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 15	Innovative Pathway for medical devices	FDA public hearing
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 2	**Novartis's Gleevec** (imatinib) for GIST	PDUFA date
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 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 20	**AstraZeneca's Brilinta** (ticagrelor), an anticoagulant	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