TRENDS-in-MEDICINE

March 20, 2011

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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

- **AEGERION PHARMACEUTICALS' lomitapide**, a once-daily treatment for familial chylomicronemia (a rare, genetic, high triglyceride disorder), received orphan drug status from the FDA. Lomitapide is in Phase III testing.
- **AMARIN's AMR-101 –** The company said data from an early-stage trial (MARINE) of this treatment for high triglycerides are sufficient to file with the FDA and that the last patient visit has been completed for a key secondary trial (ANCHOR), and the trial should be finished by June 2011. Amarin plans to file by 3Q11.
- **AMERICAN REGENT's injectable products –** Several products were recalled because translucent, visible particles consistent with glass delamination were seen in some vials. Potential adverse events after intravenous administration include damage to blood vessels in the lung, localized swelling, and granuloma formation.
- **AMYLIN PHARMACEUTICALS' Symlin (pramlintide) and TAKEDA PHARMACEUTICAL's metreleptin –** A Phase II trial of a combination of these two injectable obesity treatments was suspended to investigate a new "antibody-related laboratory finding" in two patients that suggested metreleptin may lose its effectiveness. In an earlier trial of the combination, patients lost an average of 25 pounds in 24 weeks.
- **ASTELLAS PHARMA** is buying **Maxygen**'s stake in the companies' joint venture, **Perseid Therapeutics**, which develops protein-based drug candidates to treat autoimmune conditions such as rheumatoid arthritis and transplant rejection.
- **COVIDIEN's Pipeline embolization device –** The FDA's Neurological Devices Advisory Committee voted unanimously that this flexible endovascular device is both safe and effective for the treatment of large (10-25 mm) or giant wide-necked cerebral aneurysms.
- **DEPOMED's Gralise (gabapentin) –** Depomed and **Abbott Laboratories** ended their licensing agreement, and Depomed is getting the rights to this once-daily drug for pain associated with shingles back from Abbott. Gralise was approved by the FDA in January 2011, and Depomed plans to start selling it by the end of 2011.
- **EDWARDS LIFESCIENCES** acquired **Embrella Cardiovascular**, which developed a single-use, disposable embolic protection device with a CE Mark that potentially could be paired with Edwards' percutaneous aortic valve, Sapien.
- **GEN-PROBE –** Batches of several AccuProbe test kits – the Mycobacterium Tuberculosis Complex, Group B Streptococcus, Mycobacterium Avium Complex Culture Identification Tests – were recalled because they may contain tube components that are partially

empty or empty of solution, which could cause false-negative results leading to serious adverse consequences and/or death.

- **HUMAN GENOME SCIENCES** will collaborate with **FivePrime Therapeutics** to develop FP-1039 to treat several types of cancer.
- **IMPAX LABORATORIES' IPX-066**, an extended-release carbidopa-levodopa, met the primary endpoint in a 471-patient Phase III trial in Parkinson's disease vs. immediate-release carbidopa-levodopa.
- **INCYTE and NOVARTIS's ruxolitinib (INCB-018424)**, a JAK1/2 inhibitor, met the primary endpoint in a second Phase III myelofibrosis trial, reducing spleen size. Incyte said ruxolitinib was more likely to have ≥35% reduction in spleen size at 48 weeks than placebo. This 219-patient trial, which was conducted by Novartis, is the pivotal trial for submission to European regulators in 2Q11.
- **LANTHEUS MEDICAL IMAGING's flurpiridaz F-18** – The company reached agreement with the FDA on a special protocol assessment under which it will conduct two Phase III trials for myocardial perfusion using PET imaging of flurpiridaz F-18 in patients with suspected/known coronary artery disease. The first Phase III trial is expected to start in 2Q11. Data from a completed Phase II trial will be presented at the ICNC10 - Nuclear Cardiology and Cardiac CT conference in Amsterdam in May 2011.
- **Psychiatric medications** – A bill being considered by the Indiana legislature would cut the state's Medicaid costs by creating a "preferred" list of psychiatric drugs, which would limit access to some antidepressants, attention-deficit disorder drugs, and other psychiatric medications.
- **QUEST DIAGNOSTICS** is acquiring **Celera**, which will boost Quest's biomarker work. The transaction is expected to close at the end of April 2011.
- **REGENERX BIOPHARMACEUTICALS' RGN-352** – A Phase II trial of this injectable drug for heart attacks was put on clinical hold because the FDA found a RegeneRx contractor did not comply with good manufacturing practice standards.
- **ROCHE** acquired **PVT**, which provides customized automation and workflow solutions for *in vitro* diagnostic testing in large commercial and hospital laboratories.
- **SANOFI-AVENTIS's ActHIB vaccine** – The company recalled 200,000 doses of this children's vaccine in Japan after an unidentified "foreign matter" was found in two syringes. The recall was described as a "precautionary measure" and not related to a temporary ban on the vaccine in that country.
- **SCOLR PHARMA's extended-release pseudoephedrine** was rejected by the FDA, which cited concerns about the design and conduct of the clinical trial for the company's abbreviated new drug application (ANDA).
- **TOLERX and GLAXOSMITHKLINE's otelixizumab** failed to meet the primary endpoint in the Phase III DEFEND-1 trial in Type 1 diabetes. The companies suspended a similar Phase III study pending review of the failed study.

NEWS IN BRIEF

Drug labels could get simpler – proposal for simpler labeling

U.S. Pharmacopeia (USP), the non-profit organization that sets quality and safety standards for drugs approved by the FDA, wants to simplify, clarify, and standardize drug labels. USP is hoping state pharmacy boards across the country will adopt its proposals, which seem to be common sense:

- Place patient information and instructions at the top of the label in bigger type than the doctor or pharmacy name or information on refills and expiration.
- Use common words like "high blood pressure" instead of the more technical words, like hypertension.
- Keep auxiliary information, such as warnings, simple and straightforward.

HUMAN GENOME SCIENCES and GLAXOSMITHKLINE's Benlysta (belimumab) – FDA approved but still unanswered questions

In a telebriefing for healthcare providers, FDA officials said there are still unanswered questions about this newly-approved treatment for systemic lupus erythematosus (SLE), including:

- Efficacy and safety in African Americans. An FDA clinical pharmacist, Lenore Coleman, PharmD, said African Americans are at a 3-fold increased risk for lupus, but, based on the reported Benlysta data, the drug does not appear to be efficacious, and its safety is uncertain. She also expressed concern about whether this message is getting to physicians and patients: "What steps are being taken in terms of the promotion of this drug nationally to physicians regarding the lack of African American patients in these studies?"
- The effect in patients with lupus nephritis.
- A possible waning of effect over time.
- The effect in patients with central nervous system manifestations of the disease.
- Efficacy and safety in pediatric patients and pregnant women.

Leptin – does not improve insulin sensitivity

In contrast to earlier studies, a small (18-patient) exploratory study, published in ***Diabetes***, found that recombinant leptin (r-methionyl human leptin) – at either 30 mg/day or 80 mg/day – had no significant effects on insulin sensitivity in obese patients with Type 2 diabetes over a 14-day period. Although serum leptin increased, there was no significant impact on insulin-controlled suppression of glucose, glycerol, or palmitate. The researchers concluded, "A small amount of leptin is important for normal insulin action, but increasing leptin availability above normal plasma concentrations does not have weight loss-independent effects on insulin action."

LILLY/AVID RADIOPHARMACEUTICALS' Amyvid (florbetapir) – FDA wants training program before approval

The FDA sent Lilly a complete response letter, saying that it will not approve this beta amyloid imaging agent for the early diagnosis of Alzheimer's disease until the company establishes a training program meeting specific criteria to assure that doctors accurately and consistently interpret the scans – which is what the FDA's Peripheral and Central Nervous System Drugs Advisory Committee recommended.

LILLY and DAIICHI SANKYO's Effient (prasugrel) – TRIGGER-PCI trial halted

The companies stopped the TRIGGER-PCI trial for futility. The trial was using platelet reactivity testing to guide therapy between Effient and Sanofi-Aventis's Plavix (clopidogrel) in stable angina patients. After a drug-eluting stent was implanted, poor clopidogrel responders by Accumetrics' VerifyNow test were assigned to Effient. An interim analysis of 400 of the planned 2,150 patients failed to find any significant differences between the two drugs.

Several reasons for the failure have been proposed, including:

- The event rate in both arms was so low that the trial would have required too many patients. This was the companies' theory.
- The patients may have been too low risk.
- It may be that platelet resistance testing is simply not important.

NOVO NORDISK's IDegAsp – positive early results

An early trial found this once-daily combination of NovoLog (insulin aspart) + insulin degludec was safe and well tolerated, with comparable rates of hypoglycemia but better postprandial glucose control to **Sanofi-Aventis**'s Lantus (insulin glargine). The results of the randomized, 16-week, 178-patient, open-label, proof-of-concept trial, which added IDegAsp to metformin in Type 2 diabetics, were published in ***Diabetes Care***.

NOVOCURE's NovoTTF – lukewarm FDA panel

The FDA's Neurological Devices Advisory Committee voted 7-6 that this device that blasts glioblastoma multiforme (GBM) tumors with an electrical field is effective, but panel members agreed unanimously that the device is safe, and they voted 7-3 with 2 abstentions to recommend approval for use by patients who have exhausted surgery, chemotherapy, and radiation therapy. In the 237-patient pivotal trial, NovoTTF, which is approved in Europe, missed its primary endpoint, failing to improve survival post-chemotherapy (6.3 months vs. 6.4 months with chemotherapy alone).

Opioids – abuse grows, tracking efforts stall

- ***Florida.*** The state rejected an offer of $1 million from **Purdue Pharma** to fund a state database for tracking opioid prescriptions. Despite a serious drug abuse problem in the state, Florida Gov. Rick Scott and several legislators are opposed to starting a tracking system, saying it lacks long-term funding and threatens medical privacy. However, Florida Attorney General Pam Bondi still appears to support an opioid tracking system, and a state Senate committee unanimously approved the Pill Mill Crackdown Act of 2011, which includes a provision for Florida to share data from its proposed tracking system with other states.
- **Maryland.** Admissions to treatment facilities in the state for prescription opiate abuse increased 106% from 2007 to 2010. Furthermore, in 2010, 55% of intoxication deaths involved a prescription opiate. The state does not have a prescription tracking program, but the legislature is considering a bill that would incorporate monitoring to prevent doctor shopping.
- **New York City.** More than one million oxycodone prescriptions were filled in the city in 2010 vs. half that amount in 2007.

PFIZER/KING PHARMACEUTICALS' Embeda (extended-release morphine + naltrexone) – recalled

All Embeda has been voluntarily recalled from the U.S market due to a "stability issue." Pfizer said the capsules failed to meet a pre-specified stability requirement during routine testing and now will "not be available until the issue is resolved…It is

likely that Embeda will not be available for many months." However, Pfizer insisted it intends to resolve the issue and return Embeda to the market eventually.

The recall actually started late in 2010, but it didn't get much attention until this week when a letter about the recall from Pfizer to the American Academy of Pain Medicine began circulating. Asked why this recall remained under the radar for so long, an FDA official said, "The Embeda recall was a Class III recall, which is by definition not a serious hazard to health."

When does the FDA issue a public warning? The FDA said, "The purpose of a public warning is to alert the public that a product being recalled presents a ***serious hazard to health***. It is reserved for urgent situations where other means for preventing use of the recalled product appear inadequate."

The FDA also noted that when a company decides to issue its own recall notice, the recall strategy can involve either of these approaches:

- General public warning through the general news media, either national or local.
- Public warning through specialized news media, such as professional or trade press, or to specific groups, such as physicians or hospitals.

Phase I clinical trials – national registry suggested

David Resnik, PhD, of the National Institute of Environmental Health Sciences and Greg Koski, MD, PhD, of Harvard University wrote in a commentary in the ***Journal of the American Medical Association*** that the U.S. needs a registry of all patients in Phase I studies to protect the participants from the risks of overlapping enrollment and to promote data integrity. While some states have registries, there is no national registry, and these experts recommended a national registry linked to databases available to investigators, funded by sponsor fees, and mandated by the FDA and the National Institutes of Health (NIH).

REGULATORY NEWS

CMS not changing ESA coverage

The Centers for Medicare and Medicaid Services (CMS) declined to propose a national coverage decision for when the government should pay for anemia drugs, which would leave coverage determinations to Medicare regional contractors. The review – and a MedCAC panel – began after a study suggested higher doses of anemia drugs can increase the risk of stroke and heart attack in patients with kidney disease. There is a public comment period before CMS issues a final decision, which is expected in June 2011.

CMS to check healthcare's ICD-10 readiness

CMS asked the Office of Management and Budget (OMB) to conduct surveys to monitor the healthcare industry's transition to ICD-10, which goes into effect on October 1, 2013. CMS prepared an education and communication campaign to support the adoption of, and transition to, ICD-10 and wants the OMB survey data to help it target its outreach and education efforts.

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 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	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 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 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 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