TRENDS-in-MEDICINE

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Quick Takes

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

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SHORT TAKES

- **AICURIS' letermovir (AIC-246)** for human cytomegalovirus (hCMV) was granted fast track status by the FDA. It already has orphan drug status in Europe.
- **ASTELLAS PHARMA's mirabegron** was submitted to both the FDA and European regulators as a once-daily treatment for overactive bladder. It was approved in July 2011 in Japan, where it is sold as **Betanis**.
- **ASTRAZENECA's Crestor (rosuvastatin)** failed to beat **Pfizer's Lipitor** (atorvastatin) in the head-to-head, 1,385-patient SATURN trial on the primary endpoint of percent change from baseline in atheroma volume. The company said there was a trend in favor of Crestor, but the results were not statistically significant. The full results will be presented at the American Heart Association meeting in November 2011.
- **AVITA MEDICAL's ReCell Spray-On Skin** received an investigational device exemption (IDE) from the FDA for a 20-patient, 24-week feasibility study in the treatment of hypertrophic dyspigmented scars. The company also is conducting a study of ReCell to treat acute burn wounds.
- **CHUGAI PHARMACEUTICAL** licensed from **Roche** the Japanese rights to both the humanized anti-Met antibody MetMAb for non-small cell lung cancer (NSCLC) and the humanized anti-interleukin-13 (IL-13) antibody lebrikizumab for bronchial asthma. Chugai already has started Phase I trials and will develop them with Roche's companion diagnostic tests, a met test for MetMAb and a periostin test for lebrikizumab.
- **DELCATH SYSTEMS' Chemosaturation System** – A Phase II trial of this system to deliver chemotherapeutic treatments directly to the liver by means of an artery in colorectal cancer patients whose cancer had metastasized to the liver was inconclusive, but the company said it would do additional studies.
- **DENDREON** said the FDA approved a third facility, this one in Atlanta, to make **Provenge** (sipuleucel-T), an immunotherapy for prostate cancer. *However, supply already exceeds demand.*
- **LILLY** reportedly is negotiating to purchase a minority stake in **Mustafa Nevzat İlac Sanayii AS**, a generic drug company in Turkey.
- **MEDTRONIC's SynchroMed II implantable drug infusion pumps** – The FDA issued a second Class 1 recall notice. However, Medtronic said the FDA approved a battery design change intended to prevent the issue from occurring in new pumps, and all SynchroMed II pumps are being manufactured with the new battery.

- **MERCK's Saphris (asenapine)** – The FDA issued a warning that serious allergic reactions have been reported with the use of this atypical antipsychotic for schizophrenia and bipolar disorder and that it should not be used in patients with a known hypersensitivity to the drug. The FDA said it had identified 52 cases of Type 1 hypersensitivity reactions (the most severe) in its Adverse Event Reporting System (AERS) database. Between the time of approval in August 2009 and June 2011, ~235,000 Saphris prescriptions were dispensed.
- **NUPATHE's Zelrix (transdermal sumatriptan)** – The FDA rejected approval of this migraine patch, issuing a complete response letter that cited safety, chemistry, and manufacturing issues and asked for additional data. NuPathe said additional studies, perhaps even a Phase I trial, may be needed.
- **OPTUM**, a health services firm, bought **Axolotl Corp**.
- **RAPID PATHOGEN SCREENING's Adeno Detector** – A 6-month clinical trial of this conjunctivitis test is scheduled to begin this fall.
- **SALIX PHARMACEUTICALS and PROGENICS PHARMACEUTICALS' Relistor (methylnaltrexone injection)** – The FDA accepted the supplemental new drug application (sNDA) for this injectable therapy for opioid-induced constipation in terminally ill patients. The PDUFA date is April 27, 2012.
- **STRYKER** is buying **Concentric Medical**, which makes devices (e.g., Retriever) to remove embolisms in the brain associated with an acute ischemic stroke.
- **THERMO FISHER SCIENTIFIC's** purchase of **Phadia**, a Swedish blood test company, was approved by the European Commission.
- **UNITEDHEALTH GROUP** is buying the management arm of **Monarch HealthCare**.
- **VALEANT PHARMACEUTICALS** is buying **Afexa Life Sciences**, a Canadian pharma.
- **Valproic acid** – A retrospective analysis published in ***Neurology*** found this anti-seizure drug boosts survival in glioblastoma patients when added to their standard chemotherapy – **Merck's Temodar** (temozolomide) – and radiotherapy.
- **Vesicular stomatitis virus (VSV)** – According to a report published in the ***Journal of Virology***, Yale University researchers believe an oncolytically-enhanced version of this rhabdovirus (VSV-rp30a), which is in the rabies virus family, may help in the treatment of soft tissue sarcomas.

NEWS IN BRIEF

ACTELION's macitentan – failed in IPF, still hope in PAH

The double-blind, multicenter, 14-month Phase II MUSIC trial of macitentan 10 mg vs. placebo in 178 idiopathic pulmonary fibrosis (IPF) patients failed to show efficacy, and development of this dual endothelin receptor antagonist in IPF is being abandoned.

However, the drug was safe with no increase in liver enzyme elevations. ALT >3xULN was 5.1% with placebo and 3.4% with macitentan. In contrast to other endothelin receptor antagonists, headache, hypotension, nasopharyngitis, rhinitis, and hot flush were not a problem with macitentan.

The company is continuing development in pulmonary arterial hypertension (PAH) with the Phase III SERAPHIN trial, which is fully enrolled and expected to have results in 1H12.

Clinical trials – concern over surrogate and composite endpoints

Increasingly, clinical trials of new drugs are using surrogate and/or composite endpoints rather than survival (all-cause mortality) as the primary endpoint. A study published in the ***Journal of General Internal Medicine*** analyzed >300 drug trials and found 37% used surrogate endpoints and 34% used composite endpoints as their primary endpoints. Even when mortality was the primary endpoint, 27% of the trials used disease-specific mortality, not all-cause mortality.

The authors also found trials using surrogate endpoints and disease-specific mortality as the primary endpoint were: (a) more likely to be commercially funded, and (b) more likely to report positive results.

NOVARTIS

- **Ilaris (canakinumab).** The FDA rejected this drug for gouty arthritis, issuing a complete response letter that asked the company to conduct a risk:benefit analysis in a subset of patients with gout.
- **Novartis/Sandoz's Omnitrope (somatropin).** The FDA approved this biosimilar version of Pfizer's human growth hormone, **Genotropin**, for a sixth indication, so it is now approved in the U.S. for all the same indications as Genotropin.
- **Reclast (zoledronic acid).** The FDA announced a new contraindication for use of this bisphosphonate for osteoporosis and updated the label to warn about the risk of renal

failure. The Agency received reports of renal failure leading to dialysis and even death. However, this update applies only to Reclast and not to **Zometa**, the brand name used for cancer-related indications, because the warning is already in that label.

ROCHE/GENENTECH's Avastin (bevacizumab) – repackaging warning

The FDA warned healthcare professionals of a potential eye infection risk when Avastin is repackaged and used to treat macular degeneration and other eye disorders. Initially, the FDA said there were a "cluster" of serious *Streptococcus endophthalmitis* infections in the Miami FL area from repackaged Avastin used for intravitreal injections, and there have since been reports in two other states, Tennessee and California.

In Florida, the tainted injections were traced to a single pharmacy in Hollywood FL that supplied several eye clinics from a single lot of Avastin. At least 12 patients were affected in Florida, four in Tennessee, and five at the Veterans Affairs medical center in Los Angeles. Some of the patients lost all of their remaining vision.

SANOFI's Multaq (dronedarone) – under review by European regulators

The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) met in a special session on September 2, 2011, to discuss the ongoing review of risk:benefits of this atrial fibrillation drug. The review centered on questions about liver damage, cardiac toxicity, and pulmonary effects. Apparently, no decision will be made until the regularly scheduled CHMP meeting on September 19-22, 2011.

Silicone breast implants – national registry proposed

After a two-day meeting, the FDA's General and Plastic Surgery Devices Advisory Committee:

- Recommended all women getting silicone gel breast implants be entered into a national registry that will follow them for at least 10 years post-procedure.
- Concluded the data collection requirements in the current postmarketing trials (which include an annual 25-page patient questionnaire) being conducted by **Allergan** and **Mentor** are too onerous, but the FDA is likely to continue to require that those studies be completed.
- Recommended future postmarketing studies not suggest or require an MRI every three years in women with no apparent problems. However, according to the FDA, an MRI is still the best way to detect implant ruptures, *so the likelihood of the FDA accepting this recommendation is low.*

REGULATORY NEWS

CMS issued changes to final e-prescribing rule

Healthcare providers complained, and it seems the Centers for Medicare and Medicaid Services (CMS) listened. In new e-prescribing rules for the Medicare Electronic Prescribing (eRx) Incentive Program, to be published in the Federal Register on September 6, 2011, CMS will recognize more hardship exemptions for providers and give them more time to apply for the exemptions (until November 1, 2011).

FDA guidance on pill splitting

The FDA issued guidance for brand name and generic drug-makers to ensure tablets that are scored for splitting deliver at least the minimum approved dosage in each of the split parts.

FDA's "Mini-Sentinel" pilot program up and running

The FDA announced its Mini-Sentinel safety pilot program is operational. Mini-Sentinel is the FDA's first step toward building a nationwide rapid-response electronic safety surveillance system for drugs and other medical products. Although it is named "mini," the project isn't that small; it includes 17 data partners across the U.S. and data on almost 100 million patients.

Proposed FDA review changes

The FDA's current authorization expires on September 30, 2012, and the FDA's recommendations for Congressional reauthorization reportedly include:

- a 6% increase in review fees.
- extending review times that were 6 months to 8 months and extending those that were 10 months to 12 months.

FDA approvals/clearances

- **AXIS-SHIELD's anti-CCP Elisa kit** to detect rheumatoid arthritis received 510(k) clearance.
- **IMMY's CrAg Lateral Flow Assay** to detect cryptococcosis neoformans, which can cause fungal meningitis, was cleared.
- **MEDSHAPE SOLUTION's DynaNail Intramedullary Fusion Nail**, for use in bone joint fusions, received 510(k) clearance.

- **NIDEK's MC-500 Vixi laser photocoagulator** received 510(k) clearance to treat multiple eye diseases.
- **OPTOS' Project Daytona** retinal scanning device received 510(k) clearance. The company plans a full U.S. release in 1Q12.
- **SPINE WAVE's StaXx XDL Expandable Device**, designed for lateral implant in spinal fusions, was cleared.

FDA recalls

- **ASTRAZENECA's Rhinocort Aqua (budesonide) nasal spray** – because it may have broken glass at the product's base.
- **BOSTON SCIENTIFIC's Innova Over-the-Wire Self-Expanding Stent System** – because of six complaints involving no deployment/partial deployment.
- **COREPHARMA's glyburide and ropinirole hydrochloride** – because glyburide 2.5mg may incorrectly have a ropinirole label.
- **PFIZER's Covera-HS ER (verapamil hydrochloride)** – because it did not conform to the dissolution specifications.
- **PHILIPS:**
  - **BrightView Gamma camera system** – because gaps between the table parts may pinch the patient.
  - **Vertical Brake Hubs component of the MX8000 Dual v. Exp Computed Tomography X-Ray System scanners** – All 412 units are being recalled because of a defect which could cause an unexpected downward motion of the table while the patient is on it.
- **SALIENT SURGICAL TECHNOLOGIES' Aquamantys 2.3 Bipolar Sealer Model #23-113-1** – because insulating material on the device shaft may separate and expose the electrical conductor and burn the patient's skin.
- **SANDOZ's metformin hydrochloride tablets 500 mg** – because the tablets may be adulterated with foreign matter.
- **TEVA:**
  - **Glipizide** – for impurities/degradation.
  - **Metronidazole** – because the tablets may contain foreign material.
  - **Propranolol HCl tablets** – because they did not conform to weight specifications.
  - **Tetracycline hydrochloride** – due to an incorrect expiration date.

FDA warning letters

PFIZER – The FDA warned Pfizer that the company website is making benefit claims for several drugs – **Lipitor** (atorvastatin), **Caduet** (amlodipine/atorvastatin), **Chantix** (varenicline), and **Norvasc** (amlodipine) – without providing the required sufficient risk information. Pfizer said it has already removed the contested content from the Lipitor website and is reviewing the other web information.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	September 2011	
September 7	Design of clinical trials for systemic antibacterial agents for the **treatment of acute otitis media**	FDA public workshop
September 8	**Johnson & Johnson's Xarelto** (rivaroxaban) for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation	FDA's Cardiovascular and Renal Drugs Advisory Committee
September 8-9	Safety of **transvaginal mesh** for pelvic organ prolapse	FDA's Obstetrics and Gynecology Devices Advisory Committee
September 9	Safety of **bisphosphonates** in osteoporosis	Joint meeting of the FDA's Reproductive Health Drugs Advisory and Drug Safety and Risk Management Advisory committees
September 12-13	**Proposed regulation of mobile health applications**	FDA workshop
September 13	**Anti-nerve growth factor (NGF)** drug class safety review	FDA's Arthritis Advisory Committee – postponed indefinitely
September 14	**Apotex's Ferriprox** (deferiprone) for transfusional iron overload	FDA's Oncologic Drugs Advisory Committee
September 16	Institute of Medicine's recommendations on replacing the **FDA's 510(k) clearance program** for medical devices	FDA public meeting
September 20	**Overview of the research program** in the Laboratory of Enteric and Sexually Transmitted Diseases, Division of Bacterial, Parasitic, and Allergenic Products, Office of Vaccines Research and Review, Center for Biologics Evaluation and Research (CBER), FDA	FDA's Vaccines and Related Biological Products Advisory Committee meeting at NIH ***via teleconference***
September 26	**Drug shortages**	FDA public workshop
September 26-27	**Tissue adhesive materials**	FDA workshop on facilitating innovation in these products
September 30	Institute of Medicine's recommendations for FDA's reform of the **510(k) device clearance program**	Public comment deadline
	October 2011	
October 12	**FDA guidance on diagnostic tests** being developed simultaneously with a drug/biologic	New deadline for industry comment
October 13	**Highly multiplexed microbiology/medical countermeasure (MCM) devices,** for identifying potential disease etiology	FDA public meeting
October 14	**GenProbe's Progensa PCA3 assay** to aid in the decision for repeat biopsy in men age ≥ 50 with ≥1 previous negative prostate biopsy.	FDA's Immunology Devices Advisory Committee
October 17	**Teva Neuroscience's Azilect** (rasagiline mesylate) for a new indication in Parkinson's disease	FDA's Peripheral and Central Nervous System Drugs Advisory Committee
October 28	**Bristol-Myers Squibb and AstraZeneca's dapagliflozin,** the first SGLT-2 for Type 2 diabetes	PDUFA date
October 28	**Pacira Pharmaceuticals' Exparel** (bupivacaine ER), a painkiller	PDUFA date
	Other 2011 meetings/events	
2H11	**Abbott's RX Acculink** carotid stent	FDA final decision expected
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
November 5	**Johnson & Johnson's Xarelto** (rivaroxaban) for stroke prevention in atrial fibrillation	PDUFA date
November 18	**Regeneron's Eylea** (aflibercept, VEGF Trap-Eye) for wet AMD	New PDUFA date
December	**Allergan's brimonidine tartrate intravitreal implant** – Phase II trial in dry AMD to be completed	Company announcement or medical conference presentation
December 8	**Antares Pharma's Anturol** (transdermal oxybutynin ATD gel), a treatment for overactive bladder	PDUFA date
December 13	**Endo Pharmaceuticals' Opana** (extended-release oxymorphone), a painkiller	PDUFA date

2012 FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
January	**Pfizer's Prevnar 13** (PCV13), a pneumococcal vaccine for adults	PDUFA date
January 28	**Eli Lilly, Amylin Pharmaceuticals and Alkermes' Bydureon** (weekly exenatide XR), an injectable drug for Type 2 diabetes	FDA decision date
February	**Alcon's tandospirone** for dry AMD – Phase III final data expected	Company announcement or medical conference presentation
February 17	**Corcept Therapeutics' Corlux** (mifepristone) for Cushing's syndrome	PDUFA date
February 28	**Pfizer's axitinib** for advanced renal cell carcinoma	PDUFA date (*approximate*)
March 27	**Affymax and Takeda's peginesatide** for anemia	PDUFA date
April 26	**Amgen's Xgeva** (denosumab) for prevention/delay of bone metastases in prostate cancer	PDUFA date
April 27	**Salix Pharmaceuticals and Progenics Pharmaceuticals' Relistor** (methylnaltrexone injection) for opioid-induced constipation	PDUFA date
April 29	**Vivus' avanafil** for erectile dysfunction	PDUFA date
April 30	**Baxter and Halozyme's HyQ** for immunodeficiency	PDUFA date