TRENDS-in-MEDICINE

October 2, 2011

by Lynne Peterson

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…

SHORT TAKES

- **4SC AG's resminostat**, a treatment for Hodgkin's lymphoma, was granted orphan drug status by the FDA.
- **ALMIRALL/IRONWOOD's Constella (linaclotide)** was submitted to European regulators to treat irritable bowel syndrome with constipation (IBS-C). It was submitted to the FDA in August 2011.
- **AMARIN's AMR-101 (omega-3 fish oil) –** The company submitted this to the FDA for approval to treat very high triglycerides and plans to submit another application later for treating lower, but still elevated, triglycerides.
- **ASTELLAS' darexaban maleate –** The company is discontinuing development of this anticoagulant, saying competition has increased [translation: **Bristol-Myers Squibb's Eliquis** (apixaban)], and it can't find a co-development/marketing partner.
- **BOEHRINGER INGELHEIM's BIBF-1120 –** A Phase I/II study found this tyrosine kinase inhibitor (TKI) was as effective as **Roche/Genentech's Avastin** (bevacizumab) in patients with metastatic colorectal cancer but had fewer serious adverse events.
- **CELGENE's Revlimid (lenalidomide) –** After reviewing three studies, the European Medicines Agency (EMA) concluded that the benefits of this drug to treat multiple myeloma and myelodysplastic syndromes outweigh the risk of developing other new cancers.
- **CELL THERAPEUTICS' pixantrone –** The company said it plans to resubmit this non-Hodgkin's lymphoma treatment to the FDA soon, based on a second independent radiology review of data from a study. That review reportedly found the data sufficiently strong, significant, and robust enough for the resubmission.
- **CHELSEA THERAPEUTICS INTERNATIONAL's Northera (droxidopa)** was submitted to treat neurogenic orthostatic hypotension to prevent falling in patients with conditions such as Parkinson's disease.
- **Clenbuterol –** China's State Food and Drug Administration banned the production, sale, and use of clenbuterol hydrochloride tablets, saying the risks outweigh the benefits. The tablets are mainly used to treat bronchial asthma, but clenbuterol has been found to be fed illegally to pigs to induce the growth of lean meat. *Hmm…Is there now a safety concern with imported pork or pig-derived products from China?*
- **CSL LTD.** said it has addressed many of the concerns raised by the FDA in audits conducted last year and this year about its vaccine manufacturing processes. The company said the FDA concerns were routine, and no new issues have come up.

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- **CUBIST's CB-183,315** – After positive Phase II results, the company said it plans a Phase III trial of this drug to treat severe diarrhea caused by *Clostridium difficile*.

- **DISCOVERY LABS' Surfaxin (lucinactant)** – The company said the FDA accepted its responses to questions the Agency had about clinical trials of this infant respiratory disease drug and expects the FDA to complete its review by March 6, 2012.

- **Electronic health records (EHRs)** – The American Academy of Ophthalmology (AAO) and **Sophrona Solutions** have partnered to help eye care providers meet CMS requirements for meaningful use of EHRs. Sophrona will provide ophthalmologists a link to AAO patient education content.

- **FOREST LABORATORIES' Lexapro (escitalopram)** – A randomized, double-blind study presented at the North American Menopause Society meeting found that this selective serotonin reuptake inhibitor (SSRI) significantly reduced the frequency and severity of hot flashes in perimenopausal women, with women taking a dose of 10-20 mg/day for two months reporting ≥50% symptom improvement.

- **GLAXOSMITHKLINE's MenHibrix (Hib & meningococcal C&Y vaccine)** was rejected by the FDA for a second time. The FDA said it needs more information.

- **HORIZON PHARMA's Lodotra (delayed-release, low-dose prednisone)** was submitted to the FDA to treat rheumatoid arthritis.

- **HPV testing** – Roche was awarded an exclusive contract by Karolinska University Hospital in Stockholm, Sweden, to provide a diagnostic tool for primary screening of human papillomavirus (HPV) in Swedish women.

- **HUMANA** is buying **MD Care**, a California health maintenance organization (HMO) with ~15,000 Medicare beneficiaries in four southern California counties.

- **IMMUNOGEN's IMGN-529** – The company submitted an application to the FDA seeking approval to start a Phase I trial of this treatment for non-Hodgkin's lymphoma and chronic lymphocytic leukemia (CLL).

- **MEDCO HEALTH SOLUTIONS** bought **Celesio AG**'s services program for chronically ill patients, ending a 15-month partnership.

- **MELA SCIENCES' MelaFind** – The FDA issued an approvable letter for this device for assisting in the diagnosis of skin cancer, but the Agency apparently wants additional data. MelaFind already is cleared for use in Europe.

- **MESOBLAST** is forming a manufacturing alliance with **Lonza Group**, under which Lonza may build a dedicated manufacturing plant to produce Mesoblast's stem cell treatments for spinal cord injuries and heart failure.

- **Migraine therapies** – The National Institutes of Health (NIH) gave Cincinnati Children's Hospital a $12 million grant to conduct the first clinical trial to determine the medication of choice for preventing migraines in children and teens.

- **NOVO NORDISK's degludec insulin** (an ultra long-acting insulin) **and degludec-Plus** (degludec insulin + insulin aspart) were submitted to both the FDA and European regulators to treat Type 1 and Type 2 diabetes.

- **ONYX PHARMACEUTICALS' carfilzomib** – The company finished its submission to the FDA for this drug to treat multiple myeloma.

- **ROCHE/GENENTECH and CHUGAI's Avastin (bevacizumab)** – The Japanese Ministry of Health, Labor, and Welfare approved this anti-VEGF therapy to treat inoperable or recurrent breast cancer. Previously, European regulators decided that the benefits are sufficient to allow continued marketing for this indication. However, the FDA continues to move to strip the drug of this indication, saying the efficacy was not proven.

- **SHIRE's ProAmatine (midodrine)** – Shire no longer makes this drug, which it sold for 15 years under a temporary approval, but the company still wants the FDA to grant final approval. The problem is the five companies that currently make and sell generic midodrine cannot get FDA generic approval without a brand reference. And the FDA wants patients to continue to have access to the drug. But the FDA said Shire's clinical trials do not meet its standards for approval. *How this gets resolved should be interesting.*

- **SOPHARMA's Tabex (cytisine)**, used only in Eastern Europe and licensed to **Extab**, a U.S. firm, showed promise as a cheap smoking therapy in a study published in the ***New England Journal of Medicine***. In the study, 8.4% of patients taking Tabex for 25 days with "minimal" counseling abstained from smoking for a year vs. 2.4% of placebo patients. The main side effect was gastrointestinal upset.

- **TARIX PHARMACEUTICALS' TXA-127** was granted orphan drug status in pulmonary arterial hypertension (PAH) by the FDA. The drug already has orphan drug status for treating myelodysplastic syndromes and engraftment in patients undergoing stem cell transplant.

- **TEVA** is ending its joint venture with **Kowa Company**, buying out Kowa.

NEWS IN BRIEF

BAYER's Yaz, Yasmin, and Beyaz (drospirenone) – FDA still concerned and reviewing safety

The FDA said it is still unable to reach a conclusion about the safety of oral contraceptives containing drospirenone, even after a review of two 2011 studies that found an elevated risk of blood clots, and the Agency remains concerned.

A preliminary analysis of an ongoing FDA-funded study found a ~1.5-fold increased risk vs. other hormonal contraceptives, but even that didn't resolve the issue for the FDA, so the Agency is continuing its review and has scheduled a joint meeting of the FDA's Reproductive Health Drugs Advisory Committee and its Drug Safety and Risk Management Advisory Committee on December 8, 2011, to discuss the issue. The next day the same joint panel will consider the blood clot issue with **Johnson & Johnson/Janssen's Ortho Evra** (norelgestromin/ethinyl estradiol), a transdermal system.

EDWARDS LIFESCIENCES' Sapien – CMS to cover this percutaneous aortic valve

The Centers for Medicare and Medicaid Services (CMS) initiated a national coverage decision (NCD) for transcatheter aortic valve implantation (TAVI) ***before*** the FDA even made a decision on Sapien. That's because the American College of Cardiology (ACC) and the Society of Thoracic Surgeons (STS) requested coverage. Anyone (not just the manufacturer) can ask for a Medicare NCD on a drug or device, even before FDA approval, provided that (1) there are good clinical data and (2) the data have been published in a peer-reviewed medical journal.

The CMS coverage proposal does not mean the FDA has made a decision to approve Sapien, though that is expected. The proposed NCD estimates 5,000 valves will be implanted per year, which is probably a first-year estimate only, but it appears to indicate that the societies and CMS intend for this to be a controlled uptake. In line with that, CMS also is requiring that ***all*** Sapien patients be put in a **mandatory** registry, which will help to ensure that off-label use is limited. To qualify for coverage, patients must meet the criteria used in the PARTNER trial, and physicians and centers must be trained on the devices. Exactly what that training involves is not clear, but it will be spelled out in a consensus statement from the medical societies soon.

The proposed NCD is open for public comment until October 28, 2011, and CMS plans to publish a decision memo on March 28, 2012, and a final NCD on June 26, 2012.

European Multidisciplinary Cancer Congress news

- **AMGEN's Xgeva (denosumab)** delayed the onset of bone metastases in men with castration-resistant prostate cancer (CRPC) in a 1,432-patient Phase III trial by ~4 months vs. placebo. However, there was no effect on overall survival.
- **BAYER's Nexavar (sorafenib)** – Adding Nexavar to standard chemotherapy or hormone therapy for metastatic breast cancer did not extend progression-free survival (PFS).
- **NOVARTIS' Afinitor (everolimus)**, in combination with **Pfizer's Aromasin** (exemestane), extended PFS in advanced breast cancer in the 724-patient BOLERO-2 trial by nearly 7 months vs. exemestane alone.
- **ROCHE/GENENTECH**
  - **Avastin (bevacizumab)**, when added to gemcitabine and carboplatin, extended PFS in the 484-patient OCEANS trial. PFS improved 48% in women with platinum-sensitive ovarian cancer, and even more (64%) in women who were only partially sensitive to platinum.
  - **Herceptin (trastuzumab)** and other anti-HER2 therapies did not reduce the complication rates or cost of chemotherapy in metastatic breast cancer in a study of 1,551 patients. Rates of anemia, elevated bilirubin, infection, dyspnea, neutropenia, and dehydration were comparable.

JOHNSON & JOHNSON

- **Eprex (epoetin alfa).** Oh, oh. Just when it looked like J&J's recalls were over, the company recalled two batches of this anemia medication in the U.K., Canada, Australia, and 14 other countries (not the U.S., where it is sold as Procrit). J&J claimed it was a "precautionary" action – and not the result of adverse event reports – due to a "routine" internal quality analysis that found some syringes contained drug with more or less potency than required.
- **J&J/BAYER's Xarelto (rivaroxaban).** Xarelto significantly reduced death, myocardial infarction, and stroke in the double-blind, Phase III ATLAS trial in acute coronary syndrome, according to a Bayer announcement. However, there was a statistically significant increase in bleeding. Xarelto is approved by the FDA to prevent deep vein thrombosis in patients undergoing joint replacement, and it is under review by the FDA to prevent strokes in non-valvular atrial fibrillation patients.
- **J&J/ETHICON** is buying **SterilMed**, which repairs and reprocesses medical devices.

LASIK

– FDA cracking down on misleading advertising

The FDA sent a letter to eye care professions giving them 90 days to update their advertising or promotion materials relating to LASIK to eliminate false claims. After that, the Agency plans to take regulatory action against violators. The FDA's concern is with advertising that either makes false claims or doesn't provide adequate risk information.

MERCK

- **Partnership ends.** The company sold its 50% stake in a 22-year-old joint venture with **J&J – Johnson & Johnson-Merck Consumer Pharmaceuticals**, which makes and sells over-the-counter drugs to J&J – to "focus on the consumer products business" that it acquired with **Schering-Plough**. J&J is renaming the former joint venture **McNeil Consumer Pharmaceuticals**.
- **Zolinza (vorinostat)**, which is approved to treat cutaneous T-cell lymphoma, failed to prolong survival as a second-line therapy in patients with malignant pleural mesothelioma.

Pharma drug discount programs – need better oversight

- The Government Accountability Office (GAO) said pharma programs that offer discounts to doctors and hospitals for outpatients drugs (called the 340B program) should be monitored more closely. The GAO said the Health Resources and Services Administration, which is supposed to oversee the program, has never audited it to see if it is operating as expected. *This could delay congressional consideration of an expansion of the program to inpatient drugs.*

REGULATORY NEWS

FDA issues device project list

The FDA's Center for Devices and Radiological Health (CDRH) announced a number of areas where it hopes to issue guidance in 2012. Included on this list are:

- Infusion pumps
- Artificial pancreas
- Medical devices that include antimicrobial agents
- Low glucose suspend devices
- Computer-assisted detection devices
- 510(k) modifications
- Radiofrequency wireless technology
- Framework for regulatory oversight of laboratory developed tests
- FDA notification and medical device reporting for laboratory developed tests

FDA meeting reviewed drug shortages

An FDA meeting on the drug shortage issue heard that there are >200 prescription drugs in the U.S., mostly used in hospitals, that are in critically short supply. Most (87%) of these are generic, not brand-name, drugs, and many are for oncology or anesthesia.

FDA proposed device approval reforms

The FDA issued draft guidance for manufacturers that updates and streamlines the de novo review process used for certain innovative, low to moderate-risk medical devices – e.g., certain catheters or diagnostic imaging devices – that do not meet the requirements for clearance under the 510(k) review process. The guidance outlines a pathway for a concurrent 510(k) and de novo petition without duplicative data requirements, which should cut 90 days from the review time.

FDA approvals/clearances

- **CALGARY SCIENTIFIC's ResolutionMD Mobile**, an application that allows diagnostic images to be viewed using iPads and iPhones, was cleared.
- **INFINITT NORTH AMERICA's Xelis Fusion** software, which allows PACS mergers of CT, PET, and MR images, was cleared for use.
- **SYNAPSE BIOMEDICAL's NeuRx Diaphragm Pacing System** for amyotrophic lateral sclerosis patients was granted a Humanitarian Device Exemption (HDE).

European regulatory actions

- **AVINGER's Ocelot** device, which uses optical coherence tomography (OCT) to treat patients with peripheral artery disease, was granted a CE Mark. Initially, the company plans to market it in Italy and Germany.
- **BAYER's Xarelto (rivaroxaban)** – The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) recommended two new indications for this anticoagulant: for non-valvular atrial fibrillation and deep vein thromboses (DVT). Bayer has the European rights to this drug which will be sold in the U.S. by J&J.

- **BRISTOL-MYERS SQUIBB and ASTRAZENECA's Kombo-glyze (saxagliptin + metformin)** was approved to treat Type 2 diabetes. The once-daily combination pill was approved by the FDA last year.
- **JENAVALVE's JenaValve** transapical transcatheter aortic valve implantation (TAVI) system is the first second-generation valve to get a CE Mark. The results of the pivotal 73-patient CE Mark trial are to be presented on October 3, 2011, at the European Association for Cardio-Thoracic Surgery (EACTS) meeting in Lisbon, Portugal. The primary endpoint was 30-day mortality.
- **OPTIMER PHARMACEUTICALS and ASTELLAS' fidaxo-micin** – CHMP recommended approval of this drug for *Clostridium difficile*.
- **PFIZER's Prevnar 13** – CHMP recommended this pneu-monia vaccine be approved for adults age ≥50 as well as children. The FDA is still reviewing Prevnar 13.

U.K.'s National Institute for Health and Clinical Excellence (NICE)

SANOFI's Jevtana (cabazitaxel) was rejected as a second-line treatment for advanced prostate cancer because it was determined not to be cost-effective, and NICE is uncertain about safety, especially renal and cardiac side effects.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	October 2011	
October 7	Institute of Medicine's recommendations for **standards of basic health insurance coverage through state medical insurance exchanges starting in 2014**	Report to be issued
October 12	**FDA guidance on diagnostic tests** being developed simultaneously with a drug/biologic	New deadline for industry comment
October 13	**Cook's Zilver-PTX** paclitaxel-eluting, non-polymer stent	FDA's Circulatory System Devices Advisory Committee
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 biopsyin men age ≥50 with ≥1 previous negative prostate biopsy	FDA's Immunology Devices Advisory Committee - postponed
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 25-26	**MRI safety and risk mitigation**	FDA public workshop
October 26	**AtriCure's AtriCure Synergy Ablation System** for radiofrequency AFib	FDA's Circulatory System Devices Advisory Committee
October 27	**Medtronic's Ablation Frontiers Cardiac Ablation System** for AFib via electrodes	FDA's Circulatory System Devices Advisory Committee
October 28	**Bristol-Myers Squibb** and **AstraZeneca's dapagliflozin,** the first SGLT-2 for Type 2 diabetes	PDUFA date
October 28	**Edwards Lifesciences' Sapien transcatheter aortic valve**	CMS public comment period on NCD ends
October 28	**Pacira Pharmaceuticals' Exparel** (bupivacaine ER), a painkiller	PDUFA date
	November 2011	
November 2	Discussion of regulatory, academic, and industry perspectives on the development of **anticoagulant products in children**	FDA's Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee (ODAC)
November 2	**Merck's Vytorin** (ezetimibe/simvastatin) and **Zetia** (ezetimibe), supplemental NDA to reduce major cardiovascular events in patients with chronic kidney disease (CKD), based on the results of the SHARP trial	FDA's Endocrinologic and Metabolic Drugs Advisory Committee
November 3	Clinical trial design issues related to antibacterials for **Community-Acquired Bacterial Pneumonia (CABP)**	FDA's Anti-Infective Drugs Advisory Committee
November 4	Clinical trial design issues related to antibacterials for **Hospital-Acquired Bacterial Pneumonia (HABP),** including Ventilator-Associated Bacterial Pneumonia (VABP)	FDA's Anti-Infective Drugs Advisory Committee
November 5	**Johnson & Johnson's Xarelto** (rivaroxaban) for stroke prevention in AFib	PDUFA date
November 16	**Pneumococcal 13v vaccine** safety and immunogencity in adults >age 50	FDA's Vaccines and Related Biological Products Advisory Committee
November 16	**Salix Pharmaceuticals' Xifaxan** (rifaximin) for IBS-D	FDA's Gastrointestinal Drugs Advisory Committee
November 17	**5-HT4 agonists** for chronic idiopathic constipation-predominant irritable bowel syndrome (IBS-C)	FDA's Gastrointestinal Drugs Advisory Committee
November 18	**Regeneron's Eylea** (aflibercept, VEGF Trap-Eye) for wet AMD	New PDUFA date
	December 2011	
December tba	**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), for overactive bladder	PDUFA date
December 8	**Bayer's Yaz, Yasmin, and Beyaz** (drospirenone) blood clot safety review	FDA's Reproductive Health Drugs Advisory Committee meeting jointly with the FDA's Drug Safety and Risk Management Advisory Committee
December 9	**Johnson & Johnson/Janssen's Ortho Evra** (norelgestromin/ethinyl estradiol transdermal system) blood clot safety review	FDA's Reproductive Health Drugs Advisory Committee meeting jointly with the FDA's Drug Safety and Risk Management Advisory Committee
December 13	**Endo Pharmaceuticals' Opana** (extended-release oxymorphone), a painkiller	PDUFA date
	Other 2011 events of interest	
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

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 6	**Discovery Labs' Surfaxin** (lucinactant), a therapy for infant respiratory disease	PDUFA date
March 27	**Affymax and Takeda's peginesatide** for anemia	PDUFA date
March 28	**Edwards Lifesciences' Sapien** transcatheter aortic valve	CMS expected to publish NCD decision memo
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
June 26	**Edwards Lifesciences' Sapien** transcatheter aortic valve	CMS final NCD expected