TRENDS-in-MEDICINE

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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…

Trends-in-Medicine
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SHORT TAKES

- **4SC AG's resminostat** was granted orphan drug status by the European Medicines Agency to treat Hodgkin's lymphoma.
- **APOPHARMA's Ferriprox (deferiprone)** was approved by the FDA to treat iron overload due to blood transfusions in patients with thalassemia, a genetic blood disorder that causes anemia, who had an inadequate response prior to chelation therapy. The company must do a postmarketing study in patients with sickle cell disease who have transfusional iron overload.
- **Autism** – A new California law requires health insurance companies to cover autism as a medical benefit. However, if autism is not included as an "essential benefit" under healthcare reform, then the coverage will automatically disappear when the bill expires on July 1, 2014.
- **BRISTOL-MYERS SQUIBB's Sprycel (dasatinib)** – The FDA issued a drug safety communication that some patients have developed pulmonary arterial hypertension (PAH) after treatment for more than a year with this drug for chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL). *This could have a chilling effect on use of this drug since **Novartis**' **Gleevec** (imatinib) and **Tasigna** (nilotinib) are available and do not cause PAH.*
- **CEPHALON's Spasfon (trimethylphloroglucinol)** – The French social security system reportedly is cutting reimbursement of this antispasmodic by 15%-50% on November 1, 2011.
- **COOK MEDICAL's Zilver PTX** – The FDA's Circulatory System Devices Panel of the Medical Devices Advisory Committee voted 11-0 to recommend approval of this paclitaxel-eluting stent – the first drug-eluting stent (DES) – for the treatment of symptomatic peripheral arterial disease (PAD), saying it appears safe and effective.
- **DECODE GENETICS** signed a research agreement with **Pfizer** to collaborate on efforts to find genetic variations connected to lupus.
- **DEPOMED's Serada (gabapentin)**, a medication to treat menopausal hot flashes, missed the primary endpoint in a 600-patient, 24-week Phase III trial. At 4 weeks it reduced severity and frequency of hot flashes, at 12 weeks it reduced severity but not frequency, and at 24 weeks it failed to control either frequency or severity.
- **FREEDOM MEDITECH's ClearPath DS-120 Lens Fluorescence Biomicroscope** – A 510(k) application was submitted to the FDA for this non-invasive eye scanner to identify the presence of chronic illness in patients before complications occur.

- **INSMED's Arikace (liposomal amikacin)** – The FDA refused to lift the clinical hold on this cystic fibrosis drug, saying the data are insufficient to determine the drug's risks. The FDA asked the company to conduct a 9-month toxicity test in dogs.

- **INTERCELL** plans to conduct an efficacy study of its *Pseudomonas aeruginosa* vaccine with **Novartis**, with data expected in mid-2013.

- **IVIG** – Contrary to rumors, Aetna said it is not giving preferred status to **Grifols' Gamunex** (immune globulin). Aetna will not make a coverage distinction between **Baxter's Gammagard** (immune globulin) and Gamunex.

- **K-V PHARMACEUTICAL's Makena (hydroxyprogesterone caproate, 17P)** – The American College of Obstetricians and Gynecologists (ACOG) issued a statement saying that this drug to prevent premature labor is not "identical to lower-cost compounds," so physicians "should be free to choose the version they want." Hydroxyprogesterone has been compounded by pharmacists since 1956, and Makena is much more expensive.

- **Mammography** – The governor of California vetoed legislation that would have required women with dense breast tissue to be informed of their status. Similar legislation already passed in Connecticut and Texas.

- **ONYX's regorafenib** – Onyx signed a development agreement with **Bayer HealthCare** for this multikinase inhibitor for gastrointestinal stromal tumors (GIST), which is in Phase III studies and already has orphan drug status. Bayer will pay Onyx a 20% royalty on worldwide sales of regorafenib for use in oncology and will pay Onyx $160 million for the Japanese royalty rights for **Nexavar** (sorafenib).

- **OPKO HEALTH** acquired **Claros Diagnostics**, which developed a new blood testing system for urology and infectious disease applications.

- **PFIZER's Embeda (morphine ER + naltrexone)** – **Watson Pharmaceuticals** applied for FDA approval to launch a generic version of this painkiller, but Pfizer responded with a patent-infringement lawsuit.

- **ROCHE and MORPHOSYS' gantenerumab** appeared to reduce beta amyloid plaque deposits in the brains of Alzheimer's patients in a small (16-patient) study published in the ***Archives of Neurology***.

- **ROCHE/GENENTECH's Lucentis (ranibizumab)** – The company said the 1-year results from the Phase III HARBOR trial, which was testing a 2 mg dose in wet age-related macular degeneration (AMD), did not support further studies of the 2 mg dose, and the company will be discussing 0.5 mg PRN dosing with the FDA.

- **STARPHARMA's VivaGel** – The company said the FDA has given permission for Phase III trials of this treatment for bacterial vaginosis, and those studies will begin in early 2012.

- **TAKEDA's Rozerem (ramelteon)** – The company is not going to resubmit this insomnia drug, which is approved in the U.S. and Japan, to European regulators. Takeda withdrew its original European application in 2008 after the Committee for Medicinal Products for Human Use (CHMP) recommended against approval, saying there were insufficient efficacy data.

- **TARGACEPT and ASTRAZENECA's AZD-3480** – Targacept said it will conduct a second Phase IIb trial of this Alzheimer's drug under a Special Protocol Assessment with the FDA. The first Phase II trial was inconclusive. The new 300-patient, 1-year study will compare AZD-3480 to **Pfizer's Aricept** (donepezil).

- **WARNER CHILCOTT's Doryx (doxycycline)** – The company petitioned the FDA to try to keep a generic version of this antibiotic off the market, claiming that a generic with a single score in it – compared to the double score with branded Doryx – would lead to patient confusion and suboptimal dosing. *This tactic seems a bit of a stretch.*

NEWS IN BRIEF

GLAXOSMITHKLINE's I-BET151 – possible efficacy in MLL

A study published in ***Nature*** suggests that this small molecule inhibitor may be effective in treating mixed-lineage leukemia (MLL). Researchers found that MLL depends on the binding of chromatin via BET proteins, and this BET inhibitor prevents histone binding. In the study, I-BET151 significantly improved survival in mice.

INCYTE's ruxolitinib – rebound on withdrawal

Mayo Clinic researchers reported in a letter to the ***New England Journal of Medicine*** that their independent, long-term follow-up of 51 myelofibrosis patients who received this drug in open-label trials found that withdrawal from this JAK2 inhibitor can be difficult. Serious adverse events required hospitalization in 11% of patients stopping therapy. Withdrawal symptoms included acute relapse of myelofibrosis symptoms, rapid and painful enlargement of the spleen, and acute hemodynamic decompensation, sometimes leading to reactions such as septic shock.

Furthermore, survival was not improved with ruxolitinib over standard therapy. Adverse events (including anemia and thrombocytopenia) were common, and ~50% of patients discontinued ruxolitinib within the first year – most often due to disease progression or lack of response (40%) or adverse events (34%). Only 11% were still on the drug after 3 years.

PHARMASSET's PSI-7977 – hepatitis C drug shows promise

The company expanded a trial of this experimental hepatitis C drug to include new hard-to-treat patients. The medication will be expanded to "two new groups of patients" – those "with hepatitis C genotype 1 who have not previously been treated" and "patients with genotype 2 or genotype 3 who have not been helped by other therapy regimens." The company also said it will report results from some portions of the trial on November 6 at a meeting in San Francisco of the American Association for the Study of Liver Diseases. The Associated Press explains that the announcement "is seen as a strong indication that its drug is working on the first groups of patients." Reuters (October 10, Kuber) and Dow Jones Newswires (October 11, Stynes, Subscription Publication) offer similar coverage.

TEVA – acquisition approved on two continents

- The company's takeover of **Cephalon** was cleared by the Federal Trade Commission (FTC) with several conditions, including: (1) Teva's divestiture of Cephalon's **Actiq** (transmucosal fentanyl citrate lozenges), a cancer-pain medicine, as well as Cephalon's extended-release muscle relaxant **Flexeril** (cyclobenzaprine), and (2) Teva granting permission for **Par Pharmaceuticals** to launch a generic version of Cephalon's **Provigil** (modafinil), a sleep disorder drug, next year.
- The acquisition also was approved by European regulators.

REGULATORY NEWS

Congress may tell FDA how to revise 510(k) device approvals

A bipartisan group of senators introduced legislation that incorporates many industry proposals for revising the 510(k) process for medical device approvals. The legislation:

- Takes away some of the FDA's regulatory authority.
- Eases conflict-of-interest rules that prohibited experts with financial ties to a company or a competitor from serving on FDA advisory committees provided the conflict is disclosed.
- Requires FDA officials to contract with an outside reviewer to evaluate the work of the Center for Devices and Radiological Health (CDRH).
- Requires FDA officials to "use all reasonable mechanisms to lessen review times" for products.

EU to keep ban on direct-to-consumer advertising

The European Commission is taking a strict approach to direct-to-consumer advertising of prescription medications by pharmas. The proposed changes to the rules issued in 2008 will allow pharmas to disseminate information through product labels and packaging leaflets but not copies of articles that appear in the general media. Pharmas also would be permitted to provide information on prices, clinical trials, and instructions for use, but information on websites would be very limited, and TV advertising will not be allowed.

Legislation proposed to cut Medicare drug spending

Sen. Herb Kohl (D-WI), chairman of the Senate's Special Committee on Aging, proposed legislation that would cut Medicare's payments for prescription drugs by applying Medicaid rebates to the Medicare program and would allow Medicare to negotiate prices for Part B drugs. The bill also would extend the 340B discount program that provides discounts to outpatient healthcare facilities. *Not surprisingly, pharmas oppose all three proposals.*

FDA approvals/clearances

- **BOEHRINGER INGELHEIM's Combivent Respimat**, an inhalation spray for chronic obstructive pulmonary disease (COPD), was approved as an alternative to chloro-fluorocarbon-based Combivent inhalation aerosol, which will be phased out after December 31, 2013.
- **CORMATRIX's CorMatrix ECM** was approved for vascular restoration and carotid tissue repair.

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

BRISTOL-MYERS SQUIBB's Yervoy (ipilimumab) was rejected as too expensive (at $125,600 per patient), and NICE suggested the company consider lowering the price of this melanoma therapy. NICE also noted that only 10% of patients get long-term benefit, and there is no way to identify the responders.

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 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 24	**Proposed recommendations for the PDUFA reauthorization**	FDA public meeting
October 25	Discussion of CBER's review of the use of **non-standardized allergen extracts in the diagnosis and treatment of allergic disease**	FDA's Allergenic Products 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	FDA's Circulatory System Devices Advisory Committee
October 28	**FDA's CDRH Network of Experts**	Public comment period ends
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 1	Discussion of development plans for **Adherex Technologies' sodium thiosulfate** injection, **Roche/Genentech's vismodegib**, **GlaxoSmithKline's pazopanib**, and **AstraZeneca/MedImmune's Medi-573**, and vote on **Gen-Probe's Progensa PCA3** prostate biopsy assay	Pediatric Oncology Subcommittee of the FDA's Oncologic Drugs Advisory Committee (ODAC)
November 2	Discussion of regulatory, academic, and industry perspectives on the development of **anticoagulant products in children**	Pediatric Oncology Subcommittee of the FDA's 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	Proposed changes to the **Mammography Quality Standard Act (MQSA) policies and inspection procedures**, **review of soft copy mammography images, and breast density reporting**	FDA's National Mammography Quality Assurance Advisory Committee meeting
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 Cmte
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	PDUFA date
November 27	**Transcept Pharmaceuticals' Intermezzo** (zolpidem tartrate) for middle-of-the-night insomnia	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 1	Review of **risk evaluation and mitigation strategies (REMS), including iPLEDGE for isotretinoin**	FDA's Drug Safety and Risk Management Advisory Committee meeting jointly with the FDA's Dermatologic and Ophthalmic Drugs Advisory Committee
December 1	**Contura's Aquamid**, a polyacrylamide aesthetic dermal filler for moderate-to-severe facial wrinkles, nasolabial folds, etc.	FDA's General and Plastic Surgery Devices Advisory Committee
December 7	Expanding the indication for **Medtronic's CRT-D devices** to symptomatic NYHA Class II patients with LBBB, QRS ≥120 ms, and LVEF ≤30%	FDA's Circulatory System Devices Advisory Committee
December 8	**CardioMEMS' CardioMEMS HF Pressure Measurement System,** a permanently implantable pulmonary arterial pressure measurement system	FDA's Circulatory System Devices Advisory Committee
December 8	**Antares Pharma's Anturol** (transdermal oxybutynin ATD gel), for OAB	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

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