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…

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NOTE: Subscribe to ***Trends-in-Medicine*** for coverage of the FDA's **Endocrinologic and Metabolic Drugs Advisory Committee** meeting to evaluate **Novo Nordisk's Tresiba** (insulin degludec) and **Ryzodeg** (insulin degludecPlus, or degludec/aspart) for Type 1 and Type 2 diabetes.

SHORT TAKES

- **AMYLIN PHARMACEUTICALS' Bydureon (exenatide extended-release)** – A >900-patient, 26-week, head-to-head study, DURATION-6, published in ***The Lancet*** compared two injectable GLP-1 agonists – Bydureon and **Novo Nordisk's Victoza** (liraglutide). Once-daily Victoza won on HbA_{1c} lowering (60% vs. 53% having a significant drop), but once-weekly Bydureon won on side effects (9% vs. 21% nausea, 6% vs. 13% diarrhea, and 4% vs. 11% vomiting).

- **AUXILIUM's Xiaflex/Xiapex (collagenase clostridium histolyticum)** – **Pfizer** plans to return European and Asian marketing rights to Auxilium for this drug to treat Dupuytren's contracture no later than April 24, 2013. Auxilium said it is continuing development in Peyronie's disease.

- **BIOMARIN PHARMACEUTICAL's GALNS** – The company said that the primary endpoint (increasing six-minute walk distance) was met vs. placebo for this investigational agent in the MOR-004, 24-week Phase III trial in a rare genetic disorder, Mucopolysaccharidosis Type IVA (MPS IVA), that affects about 3,000 patients worldwide. Based on these results, the company said it plans to submit the drug to the FDA in 2013.

- **CYCLACEL PHARMACEUTICALS' sapacitabine** – A Phase II study published in ***Lancet Oncology*** found that this nucleoside analog was "active and tolerable" in elderly patients with acute myeloid leukemia (AML).

- **Diabetes** – Researchers reported in the journal ***Cell Metabolism*** that people with elevated levels of SFRP4 protein in their blood have a higher risk of developing Type 2 diabetes vs. people with below-average levels, suggesting SFRP4 may be a marker for diabetes risk and may lead to the development of new diabetes drugs.

- **ICAD's Xoft Axxent brachytherapy system** – The Centers for Medicare and Medicaid Services (CMS) more than doubled the reimbursement for intraoperative radiation therapy procedures using this device.

- **INVISIBLE SENTINEL's Veriflow assay**, a pocket-sized device for detecting *Campylobacter* bacteria commonly linked to chickens, was certified by the Association of Analytical Communities, which means the test is now recognized by the FDA and the Department of Agriculture as well as certain regulatory agencies in Europe and elsewhere.

- **KV PHARMACEUTICAL's Makena (hydroxyprogesterone caproate)** – The company settled a lawsuit that accused the Illinois Department of Healthcare and Family Services of blocking Medicaid patients' access to this FDA-approved pre-term birth drug, and now the state's Medicaid program will cover Makena.

- **LILLY's solanezumab** – At the Clinical Trials in Alzheimer's Disease (CTAD) meeting, researchers presented the results of an independent biomarker analysis of the two Phase III trials of this beta-amyloid antibody. The findings suggest that the drug had a pharmacodynamic effect in the brain and in the periphery, pulling some of the amyloid out of the brain and into the bloodstream.

- **MERCK KGAA's Erbitux (cetuximab)** – The company stopped shipping this colorectal cancer drug to hospitals in Greece because of unpaid invoices.

- **NOVARTIS' Signifor (pasireotide)** – The FDA's Endocrinologic and Metabolic Drugs Advisory Committee voted unanimously (10-0) to recommend approval of this injectable drug to treat Cushing's disease despite concerns about hyperglycemia and liver enzyme elevations.

- **NOVO NORDISK's Tresiba (insulin degludec) and Ryzodeg (insulin degludecPlus)** – The FDA's Endocrinologic and Metabolic Drugs Advisory Committee voted 8-4 to recommend approval of this basal insulin for Type 1 and Type 2 diabetes – but with a postmarketing cardiovascular safety trial.

- **OTSUKA PHARMACEUTICAL's Samsca (tolvaptan)** – Phase III data published in the ***New England Journal of Medicine*** and presented at Kidney Week found that this vasopressin receptor antagonist slowed the rise in kidney volume and slowed the decline in kidney function in patients with autosomal dominant polycystic kidney disease.

- **PARAGONIX TECHNOLOGIES' Sherpa Pak Cardiac Transport System**, a disposable device used to store donor hearts in transit, was submitted to the FDA.

- **PFIZER and EISAI's Aricept 23 (donepezil 23 mg)** – The FDA rejected a Citizen Petition by Public Citizen's Health Research Group to ban this Alzheimer's drug.

- **POXEL's imeglimin** – A 12-week Phase II study to be published in ***Diabetes Care*** found this diabetes drug was additive to **Merck's Januvia** (sitagliptin) in HbA_{1C} reduction.

- **ROCHE/GENENTECH and IMMUNOGEN's trastuzumab emtansine (T-DM1)** – The FDA granted priority review to this investigational cancer conjugate for unresectable locally advanced or metastatic HER2+ breast cancer. The PDUFA date is February 26, 2013.

- **Sulfonylureas** – A study published in ***Annals of Internal Medicine*** found that using sulfonylureas first-line in diabetes was associated with an increased risk for cardio-vascular events or death vs. metformin. The question is whether sulfonylureas are harmful or metformin is bene-ficial.

- **West Penn Allegheny Health System** – A Pennsylvania judge issued a preliminary injunction, requested by insurer Highmark, blocking West Penn from discussing partnerships with other organizations. West Penn wants out of its 2011 deal to acquire Highmark (which is under review by the Pennsylvania Insurance Department).

NEWS IN BRIEF

AMGEN's Sensipar (cinacalcet) – failed in secondary hyperparathyroidism

The Phase III EVOLVE study, published in the ***New England Journal of Medicine***, found that this calcimimetic does not reduce the risk for death or major cardiovascular events (MACE) in dialysis patients with moderate-to-severe secondary hyperparathyroidism. In the study, Sensipar prolonged the time to first parathyroidectomy by 56% vs. placebo and increased the time to a first episode of severe, unremitting hyperparathyroidism by 57%, but the adverse events – nausea, vomiting, and hypocalcemia – were more frequent, and an unadjusted intention-to-treat (ITT) analysis showed only a 7% reduction in MACE.

CVS CAREMARK – adding and subtracting covered drugs

CVS said that starting January 1, 2013, its pharmacy-benefit management (PBM) will not cover an additional 17 brand drugs (making a total of 47) for which less expensive alternatives are available.

- The new additions to the list include:
  - **Abbott's AndroGel** (testosterone gel)
  - **Allergan's Lumigan** (ophthalmic bimatoprost)
  - **Pfizer's Detrol LA** (tolterodine tartrate).
- However, CVS is removing from the list:
  - **Lilly's Axiron** (testosterone gel 1.62%)
  - **Lilly** and **Boehringer Ingelheim's Tradjenta** (linagliptin)
  - **Endo Health Solutions' Fortesta** (testosterone gel).

GLAXOSMITHKLINE

- **Mosquirix (RTS, S).** This investigational malaria vaccine failed in a Phase III trial in 6,537 African babies. However, the company said it isn't giving up on the vaccine.

- **GSK-2256098.** Preliminary findings – presented at the 24th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics in Dublin, Ireland – from an ongoing 29-patient Phase I trial found that this focal adhesion kinase (FAK) inhibitor appears to slow disease progression in mesothelioma patients with an inactive tumor suppressor gene, the NF2 gene. There were no partial or complete responses, but 14 patients had stable disease.

Mammograms – breast density statement issued

The American Society of Breast Disease (ASBD) issued a statement intended to help physicians inform women about how breast density affects breast cancer screening and cancer risk. Among the points in the statement were:

- ASBD believes that if women know their lifetime risk (which is expressed as a percentage) and whether or not their breasts are dense, they will be better equipped to understand the recommendations their physicians make – and make more informed screening decisions.

- Just as adults know their blood pressure and cholesterol measurements, ASBD thinks they should know their lifetime risk for breast cancer and their breast density.

Five states – California, New York, Virginia, Connecticut, and Texas – now require breast density results to be communicated to patients.

MERCK

- **Oxytrol (oxybutynin transdermal).** The FDA's Non-prescription Drugs Advisory Committee voted that this overactive bladder (OAB) patch (which Merck bought from **Watson Pharmaceuticals**) should ***not*** be allowed to be sold over-the-counter (OTC). The vote was 5 Yes, 6 No. The FDA is expected to make a decision on the OTC switch by the end of January 2013.

- **Suvorexant.** A new drug application (NDA) was submitted to the FDA for this investigational insomnia drug (a first-in-class orexin receptor antagonist), and it will be reviewed by the Agency's Controlled Substance Staff. If approved, the Drug Enforcement Administration (DEA) will still need to determine its schedule status. The PDUFA date is in September 2013.

PLURISTEM THERAPEUTICS' PLacental eXpanded (PLX) cells – safety issue?

At least three patients have been treated on a compassionate basis with this stem cell therapy, but two of these have died. The first, the company did not report. Then, this week another of the patients died. This time the company announced it.

Pluristem CEO Zami Aberman was quoted as saying the company "doesn't follow patients after they are released from the hospital and wasn't obligated to report the girl's death… What counts legally is whether there is an improvement in the physical condition. When we saw significant improvement in the blood count, we declared a successful treatment."

PROGENICS PHARMACEUTICALS' PSMA ADC – positive but very early data

Data from a 50-patient Phase I trial – presented at the EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics – indicated that high doses of this targeted therapy produce anti-tumor activity in refractory metastatic castration-resistant prostate cancer (mCRPC), reducing circulating tumor cells (CTCs) and PSA.

The therapy conjugates a monoclonal antibody targeting prostate-specific membrane antigen (PSMA) with a chemotherapeutic agent, monomethyl auristatin E (MMAE), a tubulin disrupter – creating a PSMA ADC – that was infused in the patients at doses ranging from 0.4-2.8 mg/kg in four 3-week cycles. One patient in Phase I died, and it was not clear if the death was related. The adverse event to watch is neutropenia. A ≤75-patient Phase II trial is now underway using the 2.5 mg/kg dose.

ROCHE/GENENTECH

- **Avastin (bevacizumab).** A National Cancer Institute-funded Phase II trial of Avastin + chemoradiation in inoperable non-small cell lung cancer (NSCLC) was stopped due to "unacceptable toxicity" (two cases of fatal hemoptysis in high-risk patients) as well as slow accrual of lower-risk patients.

- **RG-7212.** Data from a 38-patient Phase I study – presented at the EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics – found that this monoclonal antibody (an anti-TWEAK-Fn14) inhibited tumor growth in advanced solid tumors expressing Fn14, including tumor shrinkage and prolonged stable disease in advanced malignant melanoma, NSCLC, mesothelioma, kidney cancer, and biliary tract cancer. Fn14 is over-expressed in at

least 30% of several solid tumors. RG-7212 was administered IV QW or Q3W at doses from 200-3600 mg. The drug was described as having an excellent safety profile.

- **Zelboraf (vemurafenib).** A case study published in the ***New England Journal of Medicine*** reported on a patient with BRAF+ melanoma who developed proliferation of leukemic cells after treatment with Zelboraf that resolved after drug discontinuation. While Zelboraf is known to be associated with squamous cell skin cancers, this is the first published report of a link to leukemia. The Memorial Sloan-Kettering Cancer Center researchers concluded, "In light of these findings, the administration of RAF inhibitors as adjuvants will require careful monitoring. They should be used only in the context of a clinical trial."

SANOFI

- **Moving?** The company reportedly was considering a move of its headquarters out of France and into the U.K. or the U.S. in order to avoid France's new 75% tax on earnings but has decided against that.
- **Zaltrap (ziv-aflibercept).** The company is cutting the price of this colorectal cancer drug by ~50% to ~$5,500/month.

Spine registry – to track spine surgery outcomes

The North American Spine Society (NASS) said its pilot registry – funded by NASS – will start collecting data on spine treatment outcomes from 16 sites across the U.S. in December 2012. The pilot will run for 15 months and, if successful, will be converted into a permanent, nationwide registry. The registry will track: patient demographics, patient outcomes and complications, use and effectiveness of pre-operative antibiotic prophylaxis, etc.

REGULATORY NEWS

FDA approvals/clearances

- **ACCURAY's CyberKnife M6 Series**, a next-generation line of the company's radiosurgery system, was cleared for use.
- **HALT MEDICAL's Acessa system**, which uses radiofrequency (RF) ablation to treat uterine fibroids, was cleared for use.
- **INTERSECT ENT's Propel mini implant**, a second-generation, smaller version of its steroid-eluting device for treating sinusitis, was cleared for use. The company plans a limited U.S. launch this month and a nationwide release in 2013.
- **LDR's Mobi-C cervical disc system** – The company received an approvable letter from the FDA for this metal and polyethylene mobile-bearing prosthetic device for use in cervical disc replacements. The company said it expects to meet the FDA requests and gain approval next year.
- **PFIZER's Xeljanz (tofacitinib)** – A 5 mg BID dose was approved to treat moderate-to-severe rheumatoid arthritis (RA) patients who can't tolerate methotrexate or for whom it is ineffective (making Xeljanz second-line). The first JAK inhibitor to be approved for RA, Xeljanz will carry a boxed warning about serious infections, including opportunistic infections, tuberculosis, cancers, and lymphoma; and there is a risk evaluation and mitigation strategy (REMS) that includes a medication guide and communication plan to inform healthcare providers about serious risks with the drug.
- **QUANTEL MEDICAL's SupraScan 577 Laser System** received clearance.
- **TELEFLEX's Weck obturators**, reusable devices used during minimally-invasive procedures to give surgical tools access, received 510(k) clearance.

FDA recalls/warnings

- **BAXTER HEALTHCARE's Buretrol Solution Sets** – A Class I recall was issued for these non-reusable, disposable devices for administering fluids from a container into a patient's vascular system because the ball-valve feature may malfunction, allowing air to flow past the valve and enter the tubing once the pre-measured amount of fluid is completely administered to the patient. Then, the air could get into the patient's bloodstream (an air embolism), which can be fatal.
- **CHIESI FARMACEUTICI/CORNERSTONE THERAPEUTICS' Curasurf** – The FDA issued a warning letter that the company was making unsubstantiated marketing claims about this drug to treat neonatal respiratory distress syndrome.
- **ONY PHARMACEUTICALS' Infasurf** – The FDA issued a warning letter that the company was making unsubstantiated marketing claims about this drug to treat neonatal respiratory distress syndrome.

European regulatory news

- **NOVARTIS' Votubia (everolimus)** was approved by the European Commission to treat benign kidney tumors in patients with tuberous sclerosis complex (TSC).
- **UNIQURE's Glybera (alipogene tiparvovec)**, a gene therapy, was approved by the European Commission to treat a very rare disorder, lipoprotein lipase deficiency (LPLD), which affects ~1-2 in 1 million people. A one-time injection of Glybera will cost ~$1.6 million (*yes, million*). The company plans to submit the drug to the FDA.

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

NOVARTIS' Xolair (omalizumab) – NICE reportedly plans to withdraw its endorsement of this drug for severe asthma, citing new mortality data and the company's proposed dosing schedule change that makes the cost-effectiveness questionable.

Regulatory news from other countries

- ***Greece:*** European Federation of Pharmaceutical Industries and Associations (EFPIA) offered to cap the total national outpatient pharmaceutical expenditure for Greece at $3.7 billion. The trade group laid out its proposal in a letter to the Greek ministers of health and finance, asking, in return, the Greek government to commit to pay off all outstanding debts and to promise not to allow further arrears to build up. The plan includes a "clawback" provision that would affect individual pharmas if the cost ceiling is breached, based on their share of the Greek market.
- ***Latin America:*** The Mercosur trading bloc – Brazil, Argentina, Venezuela, Paraguay, and Uruguay – passed Resolution 32/12, a set of measures that would standardize the way medical device and *in vitro* diagnostics companies in the region are inspected and certified.

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
2012		
TBA	**CoAxia's NeuroFlo** catheter for treating cerebral ischemia	FDA's Neurological Devices Advisory Committee *Postponed from November 1 due to weather*
November 14	Optimization of outcomes with **ventricular assist devices** (VADs) for patients with heart failure	CMS' MEDCAC
November 28	**Johnson & Johnson's bedaquiline** to treat patients with multi-drug resistant pulmonary tuberculosis	FDA's Anti-infective Drugs Advisory Committee
November 28	Discussion of the use of **absorbable material** in a variety of medical devices	FDA Workshop on Absorbable Medical Devices: Lessons Learned From Correlations of Bench Testing and Clinical Performance
November 29	**Exelixis' cabozantinib** to treat medullary thyroid cancer	PDUFA date
December 4	Discussion (no votes) of pediatric development plans for **GlaxoSmithKline's trametinib, Threshold Pharmaceuticals' TH-302, Boehringer Ingelheim's volasertib** (BI-6727), and **Amgen's blinatumomab** (MT-103)	FDA's Pediatric Oncology subcommittee of the Oncologic Drugs Advisory Committee (ODAC)
December 5	Consideration of whether **external counter-pulsating** (ECP) **devices** and **intra-aortic balloon pumps** (IABPs) should remain Class III devices	FDA's Circulatory System Devices Advisory Committee
December 6	Consideration of whether nonroller-type **cardiopulmonary bypass blood pumps** should remain Class III devices	FDA's Circulatory System Devices Advisory Committee
December 15	**Human Genome Sciences' raxibacumab** to treat inhalation anthrax	PDUFA date
December 20	**Hemispherx Biopharma's Ampligen** (rintatolimod injection, poly I: poly C12U) to treat chronic fatigue syndrome (CFS)	FDA's Arthritis Advisory Committee
December 21	**Alexza Pharmaceuticals' Adasuve** (loxapine) for agitation associated with schizophrenia or bipolar disorder	PDUFA date
December 29	**Aegerion Pharmaceuticals' lomitapide** to treat homozygous familial hypercholesterolemia	PDUFA date
December 29	**Johnson & Johnson's bedaquiline** to treat multi-drug resistant tuberculosis	PDUFA date
December 30	**NPS Pharmaceuticals' Gattex** (teduglutide) for short bowel syndrome	PDUFA date
2013		
January 16	**Santarus' Uceris** (budesonide) for ulcerative colitis	PDUFA date (extended from October 16, 2012)
January 17	**NuPathe's Zelrix** (transdermal sumatriptan), a migraine patch	PDUFA date
January 21	**Impax Laboratories' Rytary** (IPX-066) for Parkinson's disease	PDUFA date (extended from October 21, 2012)
January 29	**Sanofi/Genzyme** and **Isis Pharmaceuticals' Kynamro** (mipomersen) for homozygous familial hypercholesterolemia	PDUFA date
January 30	**Raptor Pharmaceutical's cysteamine bitartrate** delayed-release (RP-103) to treat nephropathic cystinosis	PDUFA date
February 2	**Hemispherx Biopharma's Ampligen** (poly I: poly C12U) to treat chronic fatigue syndrome	PDUFA date
February 10	**Celgene's pomalidomide** for relapsed/refractory multiple myeloma	PDUFA date
February 24	**Dynavax's Heplisav** hepatitis B vaccine	PDUFA date
February 26	**Roche/Genentech** and **ImmunoGen's trastuzumab emtansine** (T-DM1) to treat unresectable locally advanced or metastatic HER2+ breast cancer	PDUFA date
February 28	**Lundbeck** and **Otsuka's aripiprazole depot** to treat schizophrenia	PDUFA date
March tba	**Johnson & Johnson's canagliflozin**, a SGLT2 inhibitor to treat Type 2 diabetes	PDUFA date
March 1	**Zogenix's Zohydro** (extended-release hydrocodone) for chronic pain	PDUFA date
March 17	**Bristol-Myers Squibb** and **Pfizer's Eliquis** (apixaban,) an oral anticoagulant to prevent stroke in atrial fibrillation patients	PDUFA date
March 27	**Ariad Pharmaceuticals' ponatinib** for treatment-resistant leukemia	PDUFA date
March 28	**Biogen Idec's BG-12** (dimethyl fumarate) for multiple sclerosis	PDUFA date (extended from December 28, 2012)

Upcoming FDA Advisory Committees and Other Regulatory Meetings of Interest (*items in RED are new since last week*)		
Date	**Topic**	**Committee/Event**
	more 2013	
April 11	**Sanofi/Genzyme** and **Bayer's Lemtrada** (alemtuzumab) for multiple sclerosis	PDUFA date canceled because the FDA refused to accept the filing
April 29	**Shire's Vyvanse** (lisdexamfetamine dimesylate), sNDA for ADHD treatment in children	PDUFA date
May 12	**GlaxoSmithKline** and **Theravance's Breo/Relvar** (fluticasone furoate + vilanterol) to treat chronic obstructive pulmonary disease (COPD)	PDUFA date
May 31	**DepoMed's Serada** (gabapentin extended-release), a hot-flash treatment	PDUFA date
June 20	**Dainippon Sumitomo Pharma/Sunovion Pharmaceuticals' Latuda** (lurasidone), a schizophrenia drug for use in treating bipolar disorder	PDUFA date
July 28	**Aveo Oncology** and **Astellas Pharma's tivozanib** to treat advanced renal cell carcinoma	PDUFA date