TRENDS-in-MEDICINE

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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

- **ACCURAY** is acquiring **TomoTherapy**.
- **AETERNA ZENTARIS' perifosine –** The company licensed the Japanese rights to this cancer drug to **Yakult Honsha**.
- **AMICUS THERAPEUTICS' AT-2220 –** The FDA lifted a two-year clinical hold on this treatment for Pompe disease and approved the company's Phase II trial design. Amicus plans to start the Phase II trial in 1H11 and have interim results in 2H11.
- **AMYLIN PHARMACEUTICALS/LILLY/ALKERMES' exenatide *monthly* –** In a 121-patient, Phase II study, this injectable diabetes treatment was both effective and safe, reducing HbA_{1c} by 1.3-1.5 points from baseline. This compares to an ~1.5 point drop with weekly Bydureon (extended-release exenatide), which the FDA said needs further study before approval.
- **ANULEX TECHNOLOGIES' Xclose –** The FDA sent the company a warning letter telling the company it didn't file an investigational device exemption (IDE) for this device, which is designed to repair tissue around the spine, prior to enrolling patients in a clinical trial. Xclose is classified by the FDA as a "significant risk" device.
- **ARYX THERAPEUTICS' naronapride –** The FDA told the company it won't decide on the company's request for a special protocol assessment for this gastrointestinal drug until at least July 2011, and the company reportedly doesn't have enough money to continue operating until then.
- **ASTRAZENECA's Pulmicort pMDI (budesonide) –** The company stopped production of the 100 µg and 200 µg doses of this asthma drug because of technical problems in manufacturing, saying the manufacturing problem is not related to budesonide, a glucocorticoid, and doesn't affect the company's other products. **SkyePharma** developed the formulation for the medicine, which is delivered in a pressurized metered dose inhaler.
- **BIOVEST INTERNATIONAL's BiovaxID**, a cancer vaccine, was granted orphan drug status for the treatment of mantle cell lymphoma by European regulators.
- **BRISTOL-MYERS SQUIBB** is partnering with **WuXi PharmaTech**, a Chinese pharmaceutical outsourcing company that will build a testing facility in Shanghai to perform stability studies of Bristol-Myers Squibb's drug candidates.
- **DENDREON's Provenge (sipuleucel-T) –** The FDA approved the company's request to increase production capacity for this prostate cancer immunotherapy, approving 36

additional workstations at Dendreon's New Jersey facility, which brings the total to 48. The company said it will bring the new workstations on line in a staged manner.

- **EPIZYME** has partnered with **Eisai** to discover, develop, and commercialize therapeutics targeting EZH2, an epigenetic enzyme, for the treatment of lymphoma and other cancers. This makes the fourth pharma to partner with Epizyme for its histone methyltransferases (HMTs) technology.

- **GENMAB's zalutumumab** – This monoclonal antibody targeting EGFR missed the primary endpoint in a 286-patient, open-label, Phase III study, failing to improve overall survival vs. best supportive care in patients with squamous-cell carcinoma of the head and neck who had failed platinum-based therapy (6.7 months vs. 5.2 months with control, p=0.064). Zalutumumab was shown to be safe and to delay progression. The results were published in ***The Lancet Oncology*** and presented at ASCO 2010. Researchers suggested the survival benefit may have been diminished by the use of methotrexate in the control group.

- **K-V PHARMACEUTICAL's Makena (hydroxyprogesterone caproate)**, the first and only FDA-approved version of this treatment for high-risk pregnant women, will cost ~$1,500 per injection, or ~$30,000 through a pregnancy. Before Makena, doctors had pharmacies compound hydroxyprogesterone at a cost of ~$20/injection. *Will doctors prescribe Makena on-label or follow the Avastin/AMD example and keep compounding?*

- **NOVARTIS's Reclast (zoledronic acid)** – In a letter to the FDA, Public Citizen's Health Research Group urged the FDA to alert U.S. physicians immediately about a possible link between this osteoporosis drug and renal toxicity. Five months ago, after 265 cases of kidney impairment had been reported to Canadian regulators, Novartis notified Canadian doctors and patients about the possible danger, and Public Citizen wants the FDA to make the company issue the same warning in the U.S.

- **NOVO NORDISK's insulin degludec**, given Monday-Wednesday-Friday, was as effective as Sanofi-Aventis's once-daily Lantus (insulin glargine) in an open-label, Phase II, proof-of-concept trial in 245 Type 2 diabetics that was published in ***The Lancet***. Similar drops in HbA_{1c} were achieved, and hypoglycemic events were comparable.

- **REPLIGEN's RG-2417** failed to beat placebo in a 175-patient, 8-week, Phase IIb trial in bipolar depression.

- **SALIX PHARMACEUTICALS' Xifaxan (rifaximin)** – It's official. The FDA rejected Xifaxan for non-constipation irritable bowel syndrome, asking for more data. Salix is requesting a meeting with the FDA to discuss the information the Agency wants.

- **VANDA PHARMACEUTICALS' tasimelteon**, a drug for chronic sleep disorder, received orphan drug status from European regulators. Tasimelteon already has orphan drug status in the U.S.

- **VERTEX PHARMACEUTICALS' VX-765**, given 900 mg TID, met key safety and tolerability endpoints in a 60-patient Phase II study in epilepsy. Dizziness was the only adverse event occurring more often with VX-765 than placebo.

- **Walgreens** is selling its pharmacy benefit management (PBM) business to **Catalyst Health Solutions**.

NEWS IN BRIEF

CVS lawsuit – alleges use of patient data

CVS Caremark was accused in a Pennsylvania state court lawsuit of using confidential prescription information to promote products for pharmas. The company allegedly sent letters to customers' physicians that promoted specific medications and was paid by pharmas for doing that. In the letters, CVS allegedly identified consumers by name, date of birth, and medications taken.

HUMAN GENOME SCIENCES' Benlysta (belimumab) – approved by FDA

Benlysta, which will be co-marketed by **GlaxoSmithKline**, is the first drug approved by the FDA to treat systemic lupus erythematosus in 56 years. The FDA approved it in combination with existing therapies, but noted (a) Benlysta trials "suggested but did not definitively establish" that the drug reduces the likelihood of severe flares, and (b) African Americans did not appear to respond to treatment. The FDA also warned against giving Benlysta with live vaccines. The company has agreed to conduct a study in African Americans and is required to provide patients with a Medication Guide informing them of the risks.

JOHNSON & JOHNSON

- **Weekly recall** – This week it's five lots of its Animas insulin pump for potential leaks in the pump cartridges that could lead to serious health problems and death.

- **J&J/CORDIS** – The FDA issued a warning letter about violations at the company's coronary stent plant in Puerto

Rico, saying the Cypher stents failed a design-specification test meant to ensure the stents expand in a uniform matter.

- **J&J/MCNEIL** – As *Quick Takes* predicted, the FDA and the Justice Department are shutting down the McNeil plant in Fort Washington PA that makes over-the-counter drugs for failing to comply with current good manufacturing practice requirements, which led to several recalls. The action prevents McNeil from manufacturing or distributing drugs from that facility until the FDA determines the issues are resolved.

  In addition, McNeil has been given a strict timetable to bring its facilities in Las Piedras, Puerto Rico, and Lancaster PA into compliance – *or perhaps they, too, will get shut down.* McNeil also must destroy all drugs under its control that have been recalled from all three plants since December 2009 and must retain an outside expert to inspect all three plants to determine whether the violations have been corrected.

  This is not a minor administrative matter, and it is unlikely to be resolved quickly. It is surprising that J&J allowed things to get this out of hand.

MEDTRONIC

- **FDA manufacturing issues resolved** – The company announced it has resolved the issues that led to two FDA manufacturing warning letters in 2009, one for its Minnesota plant that makes CRM products and the other for its Puerto Rican plant that manufactures neuromodulation, diabetes, and CRM products. This means FDA approvals could follow soon for the Protecta ICD, the Consulta pacemaker, new Attain ICD leads, and InterStim for fecal incontinence.
- **Amplify**, a bone graft product with the same active ingredient as Infuse (rhBMP-2), was rejected by the FDA, which issued a not-approvable letter. The company is unsure yet whether additional clinical trials will be necessary. The FDA decision also could have negative implications for use of Infuse.

NOVARTIS's Arcapta Neohaler (indacaterol) – gets approval recommendation from FDA panel

The FDA's Pulmonary-Allergy Drugs Advisory Committee voted 13-4 in favor of approval of a 75 µg QD dose of this long-acting beta agonist (LABA) to treat chronic obstructive pulmonary disease (COPD). The panel voted 12-5 against recommending approval for the 150 µg dose, which is the approved dose in Europe. The concern with the higher dose was lack of sufficient long-term follow-up showing it is safe or more effective than the lower dose.

If the FDA approves Arcapta, it would be the only once-daily LABA. In 2009, the FDA rejected all three proposed doses of indacaterol (75 µg, 150 µg, and 300 µg). The PDUFA date is in April 2011.

Opioids

- More than half a billion doses of oxycodone were distributed in Florida in 2009, up sharply from 2008 and twice as many as the No. 2 state, Pennsylvania (with 267 million pills dispensed). Overall, national distribution of oxycodone rose 11% year-to-year.
- The Colorado Senate Appropriations Committee voted against renewing the state's opioid tracking program.

PFIZER

- **Tofacitinib (formerly tasocitinib)** – The company announced that this oral JAK inhibitor for rheumatoid arthritis met the primary endpoint in a Phase III trial, reducing the signs and symptoms of the disease over six months.
- **Viagra (sildenafil)** – Daily modified-release sildenafil might have a new use – reducing the frequency of Raynaud's syndrome in patients with scleroderma. A 57-patient, double-blind, placebo-controlled trial, published in ***Arthritis & Rheumatism***, found sildenafil reduced attacks by 44% per week vs. an 18% reduction with placebo.

ROCHE

- **Rituxan (rituximab)** – A 51-patient, 24-week, placebo-controlled trial found adding Rituxan to a TNF inhibitor plus methotrexate in rheumatoid arthritis (RA) was as safe as just a TNF inhibitor, but efficacy was not increased. However, the study, which was published in ***Arthritis & Rheumatism***, was designed to look at safety, not efficacy. A larger efficacy study is under way.
- **ROCHE/GENENTECH's Avastin (bevacizumab)** – A study published in the ***Journal of Clinical Oncology*** concluded that Avastin is not cost-effective in ovarian cancer, with the incremental cost-effectiveness ratio more than $400,000 per patient.
- **ROCHE/GENENTECH's Lucentis (ranibizumab)** – Positive 24-month results from the RISE trial in diabetic macular edema (DME) were presented at the Macula Society meeting. RISE was a multicenter, randomized,

double-masked, sham injection-controlled, 36-month, 377-patient, pivotal Phase III study. The results showed significantly more patients gained ≥15 letters on the eye chart vs. baseline, which was the primary endpoint.

- Lucentis significantly improved average eye chart reading scores as early as seven days and maintained out to 24 months.
- Retinal swelling was significantly decreased.
- Safety was consistent with the expected Lucentis profile.

The study was not designed to compare the two doses of Lucentis, but it does appear that the 0.3 mg dose is sufficient, if not better.

RISE Trial Results of Lucentis in DME

Measurement	Lucentis 0.3 mg n=125	Lucentis 0.5 mg n=125	Sham control n=127
Primary endpoint: ≥15 letter gain	44.8% *	39.2% *	18.1%
Mean gain in BCVA at 24 months	12.5 letters *	11.9 letters *	2.6 letters
Mean gain in BCVA at 7 days	5.4 letters *	4.6 letters *	1.6 letters
Change in central foveal thickness	– 250.6 microns	– 253.1 microns	– 133.6 microns

* p<0.05 vs. sham

Vaccines – safety questioned in Japan

Japan's health ministry suspended the use of two pediatric vaccines – **Pfizer**'s Prevnar for meningitis and pneumonia and **Sanofi-Aventis**'s ActHIB for influenza type b – after reports of five children dying shortly after immunization. The Japanese Ministry of Health, Labor, and Welfare convened an expert panel, which did not find a causal relationship between the deaths and the vaccines but called for further studies, and the government continued the suspension. All five of the children who died had received Prevnar, and three also received ActHIB plus another vaccine at the same time. The FDA reportedly has not identified any problems with the vaccines in its Vaccine Adverse Event Reporting System.

REGULATORY NEWS

CMS changes its mind on MRIs for some patients with pacemakers and ICDs

In February 2011, the Centers for Medicare and Medicaid Services (CMS) announced it would continue to refuse coverage for MRI scans of patients with implanted pacemakers and implantable cardioverter defibrillators (ICDs) except in clinical trials, but now CMS is reconsidering its decision with respect to **Medtronic**'s Revo MRI SureScan, a pacemaker deemed MRI-safe by the FDA, as well as other 510(k)-approved MRI-safe devices.

CMS considers reimbursement for percutaneous valves

CMS's ICD-9 Coding Committee met this week to discuss transcatheter aortic valve implants (TAVI). CMS was recommending that a new code be established, and the committee asked no questions, appearing to be in agreement. This means new codes should be published in the Federal Register on August 1, 2011, and take effect on October 1, 2011.

Congress looking into drug rebates

Democrats on the House Energy and Commerce Committee called for a hearing on Medicare prescription drug rebates after the Inspector General for the Department of Health and Human Services (HHS) said his office's review "identified several concerns about these rebates."

Prescribing for psychologists?

Legislators in six states – Arizona, Hawaii, Montana, New Jersey, Oregon, and Tennessee – are considering bills that would allow psychologists to prescribe psychotropic medications, despite strong opposition from the American Medical Association, the American Psychiatric Association, state physician organizations, and others.

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 15	Innovative Pathway for medical devices	FDA public hearing
March 16	Preliminary decision on **how to cover ESAs** for kidney disease patients	CMS decision
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 7-8	**FDA 510(k) reform**	FDA 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
Other future 2011 meetings/events		
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 16	Final decision on **coverage of ESAs** for kidney disease patients	CMS decision
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